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ALLERGY AND SUBMARINE MEDICINE WITH REFERENCE TO AEROTITIS MEDIA

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THE PREDICTION and prevention of aerotitis media in candidates for Submarine School, United States Navy, is a problem that has received a good deal of attention because of the large numbers of men affected. No satisfactory explanation for this pathologic condition has been presented to date. United States Navy submarine personnel are volunteers for this type of service, and must pass a rigorous psychological, physical and educational examination to qualify in this select activity.[12-13] One of the major factors in processing submarine school candidates includes exposures to fifty pounds of air pressure in a dry pressure chamber and escape training practice from various water depths to 100 feet in the escape training tank.

Infection of the postnasal spaces, adenoid tissue, excess lymphoid tissue, dental malocclusion deformities and possible psychologic factors have been thoroughly studied in an effort to predict and prevent aerotitis. According to Shilling,[1] 27 to 30 per cent of the candidates taking these tests have suffered from some degree of aerotitis. Allergy as a possible predisposing factor has been mentioned by several investigators (Teed-Haines[3-5]) but has not been studied. The object of this study was to determine the role of nasal allergy as a prime factor in the mechanics and dynamics of aerotitis. If the allergic theory is correct, a number of favorable candidates could be salvaged for active duty as submariners.

THE PRESSURE (RECOMPRESSION) CHAMBER AND THE ESCAPE TRAINING TANK

Of the men undergoing submarine escape training at the U.S.N. Submarine Base, New London, Connecticut, 30 per cent have difficulty leading

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to aerotitis media and possible loss of auditory acuity.[2-4] They are required to "take" successfully 50 pounds (50 pounds per square inch gauge, (P.S.I.G.), 3.4 atmospheres) air pressure in a recompression chamber in three to ten minutes. This is a prerequisite for entrance into submarine school. Of the men who fail to pass this test, 82 per cent fail below the first 11 pounds of pressure. This is to be expected, for it is in this range that greatest proportionate change of air pressure occurs.

Those men who have passed the rigid physical examination and the pressure tank test are then sent to the submarine escape training tank. This is a tower containing a column of fresh clear water 25 feet in diameter and 100 feet high. Escape trunks are located at depths of 18, 50 and 100 feet, constructed in a manner similar to the escape trunk of a submarine. Men are required to enter a trunk, submit to a pressure increase appropriate to the depth of the trunk, don an oxygen-supplying and CO_2-absorbing apparatus, pass from the trunk to the water, and ascend to the surface. About 10 per cent fail this test. Those who suffer from aerotitis are given two or three more chances to pass the test. This means that these highly specialized instructors (there are often fifteen in the tank at once) must spend many extra hours in the tank repeating this hazardous work for those candidates who fail the first attempt.

PHYSIOLOGY AND PATHOLOGY OF AEROTITIS MEDIA

Aerotitis media is caused by failure to equalize pressure between the middle ear and the surrounding atmosphere. The pathology varies from slight congestion to separation or rupture of tissues. Pain, discomfort, vertigo, dizziness, plugged ear, bleeding into the middle ear, temporary hearing loss and rupture of the ear drum may result. Aerotitis media is also known as aero-otitis, aerotitis, otitic barotrauma, otic barotrauma, salpingotympanitis, and aviator's ear, among other terms.

The eustachian tube is normally closed, entrapping air in the middle ear. If the ambient air pressure is moderately increased or decreased, the automatic process of the eustachian tube, being forced open to allow air to escape or enter, equalizes the pressure and the subject is comfortable.

If the pressure continues to increase, the differential pressure keeps the tube closed instead of open.[1] If, then, the tube is not opened by action of its muscles, aerotitis of varying degrees develops, depending on the degree of differential pressure. If the tube is cleared from time to time by swallowing, yawning, sneezing, chewing, contracting the throat, or the Valsalva maneuver (forced expiration while holding the nose), while the pressure is increasing, the subject is comfortable and is able to sustain great amounts of pressure. It is only when something goes wrong with the intermittent equalization process that the typical aerotitis syndrome develops. The tube becomes "locked." Relief can only be obtained by reducing the pressure and surfacing. This is the reverse of an airman who may have aero-

titis when he descends to greater pressure on the ground than he experienced at high altitudes.

Colds or excess lymphoid tissue blocking the eustachian tube may predict trouble in the middle ear. The individual with chronic or acute allergic rhinitis usually has at one time or another a hyperplastic, edematous nasal mucosa which reacts rapidly to various physical factors, such as pressure changes. This blocks or "locks" the eustachian tube, resulting in the aerotitis syndrome. Too vigorous effort to clear the tubes may cause hyperemia of the nasal mucosa. All severely damaged ears have flattened eustachian orifices due to lymphoid hyperplasia (Shilling[2]). Deafness is usually slight and often transient.

Aero-sinusitis may also occur. A positive air pressure develops in the frontal or maxillary sinuses and the resulting barotrauma causes the mucous membranes to become edematous and hemorrhagic capillary changes may occur. Toothache occurs occasionally from air forced into cavities or loose fillings.

REVIEW OF THE LITERATURE

Many competent highly trained submarine medical officers have studied this problem. Various suggestions have been made in an effort to lower the attack rate of aerotitis. Teed[3] postulated that the rate could be lowered from 30 per cent to 2 or 3 per cent by proper preselection and a routine check of each man's ability properly to perform the Valsalva maneuver. This did not work out at that time. Haines and Harris[5] conclude that the "incidence of 15 per cent failures is a theoretical floor and that nothing has been found to predict aerotitis except previous attacks." Shilling, Peirano, Alvis, Schulte and others have tried various treatments which have not materially changed the situation. Some of these were:

1. Thorough physical examination and instruction before and after pressure chamber and escape tank tests.
2. Psychologic build-up, stressing motivation and fear. Chewing gum, music and other distractions were used.
3. Topical treatment to the nose, such as Neo-Synephrine every hour for several hours before testing.
4. X-ray treatment to the postnasal spaces.
5. Radon applicators to the same areas to reduce lymphoid tissue.

The dental theory advanced by Kelly[11] is interesting and controversial. He states that dysfunction of the temporomandibular joint could affect the normal operation of the eustachian tube. Only those cases of overclosure of the mandible were selected. Kelly claims forty-six out of fifty cases improved by treatment to correct this overclosure. Teed[3] doubts this contention.

Gantt[10] studied 103 cases thoroughly before and after the pressure tests in an effort to predict those men who will develop aerotitis and those who

TABLE I. PREDICTION OF AEROTITIS IN SUBMARINERS—PLAN FOR FINDING THE ALLERGIC CANDIDATE (GANTT)

1. History—Family and individual—past and present of Allergy
2. Physical examination of nose and throat:
   1. Mucosa—Color—Edema—Discharge
   2. Turbinates—Edema—Breathing area—Color
   3. Blowing test for stuffiness, one or both nostrils
   4. Tonsils enlarged—Regrowth tags—Normal or absent
   5. Pharynx granular—Nodular
3. Intradermal tests of a pilot group for house dust, grass, ragweed pollen, feathers, wool, molds, milk, wheat, eggs, orange, control

POSITIVE history of allergy)
Positive blowing test nares) These four findings usually indicated an allergic individual
Turbinates pale—edematous)
Skin tests—at least 3 positive)

Candidates having congested nose whether due to allergy or a "cold" have five or more times as much chance to develop aerotitis than those who are normal (nonallergic) or do not have an acute upper respiratory infection.

TABLE II. PREDICTION OF AEROTITIS IN SUBMARINERS BY HISTORY—ALLERGIC OR NONALLERGIC

	Total Cases	Normal Ears	Red Painful Ears
Allergic	37	22	15 (40%) of ALLERGIC
Nonallergic	66	57	9 (13%) of NON-ALLERGIC
Total	103	79	24 (23%)

A candidate with an allergic history has three times as much chance of developing aerotitis as a nonallergic subject.

will not. His work involves only a small number of subjects but is significant because of its thorough nature especially in reference to allergy. He found high correlations of prediction between allergy and aerotitis *before the subjects took the tests.* A positive history of allergic manifestations, the red color of the nasal mucosa, edema of the turbinates, and a positive nose blowing test (blowing first one side then the other) to note any obstruction, definitely predicted aerotitis five times as often as in those who did not have these signs. Men with normal nasal mucosa did not develop aerotitis. His conclusions were: (1) that the incidence of aerotitis is higher in those with nasal allergy, and (2) that there is a relationship between the incidence of aerotitis and pathology of the nose and one can predict a high rate of aerotitis in this susceptible group.

Schulte,[9] in a recent study of 5,000 candidates, used either a nasal decongestant or placebo drops before the tests. He found a higher degree of correlation of those passing who had used the nasal decongestant than those using the inert drops.

AUTHOR'S STUDY

Fifty candidates who suffered acute painful ears following the pressure chamber test and/or the escape diving training test were studied by the author. A thorough history, with special emphasis on allergy and upper respiratory infection, was obtained. A careful physical examination was immediately made of their ears, nose and throat. Twenty-one (42 per cent) of the fifty sailors with aerotitis had a history and physical findings of acute

TABLE III. PREDICTION OF AEROTITIS IN SUBMARINERS BY APPEARANCE OF TURBINATES AND NOSE BLOWING TEST FOR STUFFINESS

B=blowing test +means congestion one or both nares
T=turbinates +means edema —is normal

	Cases	Normal Ear	Painful Ear	
B+ T+	55	35	20	36%
B— T—	22	21	1	5%
B+ T—	19	18	1	
B— T+	7	5	2	

A positive nose blowing test (congestion) and edema of turbinates predicts aerotitis seven times more often than normal unobstructed nasal passages.

TABLE IV. PREDISPOSING CAUSES OF ACUTE AEROTITIS MEDIA—50 CASES. PRESSURE CHAMBER AND ESCAPE TANK TESTS. USN SUBMARINE SCHOOL, NEW LONDON, CONNECTICUT

ALLERGY History and Physical Examination	UPPER RESPIRATORY INFECTION Nov.-Dec.	NO APPARENT CAUSE Improper clearing Ear Tubes	PSYCHOL.
16 32%	21 42%	12 24%	1 2%

All fifty had red ear drums (varying degree) and pain.
Control group *Without* aerotitis had only a few cases of allergy or upper respiratory infection.
Allergy and/or upper respiratory infection was present in 76 per cent of the subjects who developed aerotitis.

upper respiratory infection, such as pharyngitis, tonsilitis, or sinusitis, at the time of the tests. Sixteen (32 per cent) revealed a definite history of perennial nasal allergy or hay fever (chronic sinus or chronic catarrh). Twelve men gave no apparent reason for aerotitis which was probably due to improper or too vigorous clearing the ears. One man was so scared that he did not do anything right.

The high incidence of upper respiratory infection was endemic for the season and predisposed to aerotitis. These findings compare favorably with those of Gantt. This again emphasizes that pathology involving the pharyngeal opening of the eustachian tube predisposes to aerotitis.

There were very few cases of allergy or upper respiratory infection in those passing the test who had no ear trouble.

PATHOLOGY OF ALLERGY AND RELATION TO AEROTITIS

There are three main tissue changes that occur in the development of allergic manifestations. One or all may occur in an allergic syndrome: (1) Edema of mucous membranes; (2) spasm of smooth muscles, or (3) mucus secretion in excess amounts.

Allergy and hyperplasia of mucosa and lymphoid tissue go hand in

hand. This often predisposes to the formation of hyperplastic tissue in the nasopharynx especially at the opening of the eustachian tubes.

Allergic symptoms are *caused* by *primary* allergens such as foods, epidermals, pollens, or molds. *Secondary* physical factors may *aggravate* an already existing allergic condition. These are heat, cold, wind, friction, emotions, changes in barometric pressure and increased pressure such as in a diving or snorkeling submarine. When the outside pressure is suddenly increased as in the pressure chamber or diving tank, edema of these sensitive tissues occurs, tending to obstruct the opening of the eustachian tubes. As pressure increases, spasm of the two smooth muscles (levator and tensor veli palatini[7] which control the opening and closing of the pharyngeal portion of the auditory tube) occurs and the tube is "locked." The increasing pressure from all directions causes edema and hemorrhage of tissues such as in aerotitis media.

PLAN FOR PREDICTION AND PREVENTION OF AEROTITIS

Only one of every five candidates (in Gantt's and the author's cases) were aware of the fact that they had nasal allergy in the form of hay fever or perennial allergic rhinitis. The other allergic subjects thought they had chronic catarrh or sinus trouble, "broken (baseball) nose," or believed that it was normal for their nose to be "stuffy" every night.

A careful history of the patient and his family relative to allergic symptoms, plus the physical examination of the nose and throat, with emphasis on the nasal mucosa, size of the breathing area (blowing test), and the condition of the turbinates, is usually adequate to diagnose an allergic condition. This allergic person has about 80 per cent more chance of having aerotitis than a nonallergic one. *Allergic individuals are also susceptible to motion, air or sea sickness in the same degree.* Men with normal-appearing nasal cavities and without an allergic history will seldom have trouble "taking pressure" in submarine or aviation training or transport. An upper respiratory infection also predisposes to aerotitis because of the edema, and inflammation around the eustachian tubes which is increased by trauma of pressure.

When the diagnosis of allergy or infection of the nose or throat is made, treatment to prevent aerotitis prior to the pressure tests should be instituted. This consists of two factors:

1. Nose drops, such as Neo Synephrine 0.5 per cent or Biomydrin inserted into each nostril about one-half hour and again five minutes before the test. If both nares are clear and the subject breathes freely, he should not have trouble.

2. An antihistamine in full dose one-half hour before the test is due.

The incidence of aerotitis in our small series of those who repeated the tests (who did not pass the first time due to aerotitis) can be reduced to five per cent or less.

Occasionally other factors may contribute to failing the pressure tests,

such as too vigorous or too little clearing of the ear tubes, lack of motivation, or fear.

COMMENT

The Medical Department of the Submarine Service has many important and varied problems that are peculiar to this branch of the Navy. These have now been expanded by the nuclear-powered submarine. The U. S. Navy Medical Research Laboratory at the Submarine Base, New London, Connecticut, has contributed a number of excellent original monographs in such areas as hearing, sound, vision, color effects, oxygen and carbon dioxide toxicity, health engineering, and many other medical areas as well as atomic medical problems. Many devoted, highly motivated, well-trained medical officers are contributing not only to the special problems of Submarine Medicine but to those of general medicine. The Naval Reserve officer is privileged to be able to participate in these activities by active training duty. The civilian physician may also contribute to these special military problems by his knowledge.

The problem of aerotitis and allergy is only a minor one in this large field of submarine medicine. It is hoped that this clinical study will encourage more active participation of Medical Reserve Officers in military medical problems.

ACKNOWLEDGMENT

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PARA-BROMDYLAMINE MALEATE (DIMETANE®)

A Clinical Evaluation: Report of 140 Cases

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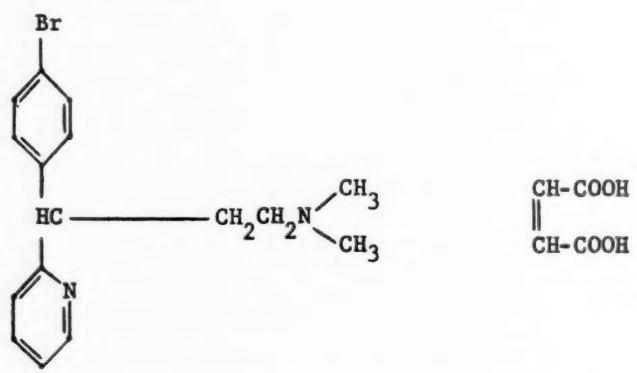
WE, who are in the practice of allergy, as well as all clinicians, are constantly on the alert for improved and worthwhile drugs to add to our therapeutic armamentarium. The antihistamines have played a major role in the symptomatic relief of many of the allergic manifestations, and certain of this improved group of drugs are found to be beneficial in other respects. We are all cognizant of the necessity of having our patients try different antihistamines, as we are aware of the fact that there are patients who show absolutely no response to one antihistamine, and when an antihistamine of a different chemical structure is employed, a favorable response is obtained. It is further observed that although a patient shows a response to an antihistamine of one group, an even better response may be obtained to a different chemical structure in the same group.

During the past two years, I have had the opportunity of observing a new antihistamine—Dimetane,®* not only in private practice but also in an out-patient clinic.

Dimetane® is a Robins' synthetic antihistaminic para-bromdylamine maleate which is 1-(p-bromophenyl)-1-(2-pyridyl)-3-dimethylaminopropane maleate.

The structural formula is:



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*The Dimetane® employed in this study was supplied through the courtesy of the Medical Department of A. H. Robins Co., Inc., Richmond, Va.

TABLE I. SUMMARY OF RESULTS OF DIMETANE® THERAPY IN PATIENTS SHOWING VARIOUS ALLERGIC MANIFESTATIONS

Allergic Manifestations	No. Patients	Dosage Per Day, in Mgs	Days of Therapy	Satisfactory Response	Dimetane® Tolerated	Dimetane® Not Tolerated
Rhinitis	10	4-36	5-40	6	8	2
Asthma	7	16-36	30-75	6	6	1
Hay fever	6	16-36	20-60	5	6	—
Urticaria and angioneurotic edema	6	16-36	2-120	6	6	—
Allergic dermatoses	18	16-36	3-250	14	16	2
Rhinitis and asthma	28	8-36	1-147	28	28	—
Hay fever and asthma	4	16-36	13-34	4	4	—
Rhinitis, hay fever and asthma	21	16-36	1-150	19	19	2
Rhinitis and dermatitis	13	16-36	3-120	12	12	1
Rhinitis and urticaria	12	16-36	2-165	11	11	1
Miscellaneous	15	16-36	1-155	11	13	2
Total	140			122	129	11

PHARMACOLOGY

Extensive studies[1] in several species of animals showed the compound to be highly potent as a histamine antagonist but of low toxicity. When compared with other extensively used antihistamines—chlorpheneramine, diphenhydramine and tripelennamine—it was unexceeded by any of them and very greatly surpassed the latter two agents.

This antihistaminic agent has previously been used by twelve clinical investigators in 175 patients with good results in various allergic manifestations.[2]

In view of the fact that there has been such an extensive consideration of hundreds of antihistamine preparations and antihistamine type drugs, we feel that it would be superfluous to present here an extensive review of the literature on the various antihistaminic agents, especially since such a review was carried out and published in 1950 by Brown and Krabek.[3,4,5]

CLINICAL INVESTIGATION

In this clinical study we have placed a group of allergic patients on the compound. Table I shows primary diagnoses followed where indicated by minor allergies. This table also shows that of the 140 patients included in this study, the largest single grouping of patients were those with both allergic rhinitis and bronchial asthma. Of those patients having a single allergic manifestation, the following was observed: perennial allergic rhinitis, ten cases; bronchial asthma, seven cases; seasonal hay fever, six cases. The allergic dermatoses include eighteen patients having either an atopic dermatitis, contact dermatitis, or dermatitis medicamentosa. The *miscellaneous* group included patients who did not fall into any of the other listed manifestations and included those patients having aphthous stomatitis, allergic conjunctivitis, gastrointestinal allergy, drug allergy (other than dermatitis medicamentosa), migraine headaches, constitutional reactions secondary to insect stings, pruritus ani, cerebral manifestations of allergy and physical allergy.

The dosage per day in milligrams varied from 4 mgs to 36 mgs. Usually those patients getting 8 mgs per day were children who were on the Elixir of Dimetane,® 2 mgs four times a day, or those patients who received a 4 mg tablet of Dimetane® in the morning and at night. We endeavored to get the patients on the smallest amount of this drug that would offer them a satisfactory response. In other instances with higher dosages up to as much as 36 mgs per day, there was no significant side reaction.

The days of therapy revealed in Table I varied from one to 250. Those patients who received therapy for the longest period of time were in the following categories: (1) allergic dermatoses up to 250 days; (2) allergic rhinitis and bronchial asthma, up to 165 days; (3) miscellaneous group, up to 155 days; (4) rhinitis, hay fever and bronchial asthma, up to 150 days; (5) rhinitis and asthma, up to 147 days; (6) urticaria and angioneurotic edema, as well as rhinitis and dermatitis—both groups received therapy up to 120 days; (7) asthma, up to seventy-five days; (8) hay fever, up to sixty days; (9) rhinitis, up to forty days; and (10) hay fever and bronchial asthma, up to thirty-four days. Dimetane was tolerated in 129 of the 140 patients and was not tolerated by eleven patients.

RESULTS

It was observed that in the group of patients having angioneurotic edema and urticaria, rhinitis and asthma, and hay fever and asthma, all reported a satisfactory response. The second most satisfactory group response was observed in those patients having rhinitis and dermatitis, rhinitis and urticaria, rhinitis and hay fever and asthma. The group showing the least satisfactory response was noted in the group of ten patients having perennial allergic rhinitis where six of the patients were improved on therapy.

In summarizing our therapeutic results, we have been impressed with the fact that, with the exception of urticaria and angioneurotic edema, those patients who have had multiple manifestations of allergy have shown a higher percentage of response to therapy than those who had a single manifestation.

In the classification of response to treatment shown in Table II a definite response to therapy was considered in those patients who reported that their symptoms were satisfactorily controlled or that were asymptomatic as a result of the therapy. Those patients who did not appreciate any change of their symptoms or an aggravation of their symptoms, totalled seventeen. It is further observed in Table II that fifty-two of the patients tolerated the compound as well as other antihistamines. Of the patients who did not tolerate previous antihistamines, seventeen were able to tolerate the antihistaminic agent. There were eight cases

TABLE II. A COMPARISON OF DIMETANE® TOLERANCE WITH THAT OF A HISTORY OF TOLERANCE TO OTHER ANTIHISTAMINICS CONSIDERED AS A GROUP—ALL PATIENTS DID NOT HAVE PRIOR THERAPY WITH OTHER ANTIHISTAMINICS IN ADDITION TO DIMETANE®

Tolerance	Number of Patients
Dimetane® tolerated	129
Dimetane® not tolerated	11
Dimetane® and other antihistaminics tolerated	52
Dimetane® tolerated, other antihistaminics not tolerated	17
Dimetane® not tolerated, other antihistaminics tolerated	8
Dimetane® and other antihistaminics not tolerated	10
Dimetane® superior to other antihistamines	63
Other antihistamines superior to Dimetane®	9

TABLE III. TYPE OF SIDE REACTIONS TO DIMETANE®

Side Reaction	Number
Drowsiness	6
Gastrointestinal discomfort	1
Nervousness	1
Urinary discomfort	2
Muscular pains or aching of legs	1
Total	11

who did tolerate other antihistamines but did not tolerate the compound. It and other antihistamines were not tolerated in ten patients.

There were sixty-three patients of the group who reported that they felt the compound under consideration offered them more relief or was superior to other antihistamines. In contrast, there were nine patients who felt that other antihistamines were superior to para-bromdylamine maleate.

Of the eleven patients who did not tolerate the compound or had annoying side reactions, only eight warranted the discontinuance of the drug, and five of the eight patients in this group were unable to take any antihistamines, regardless of type.

These side reactions experienced with para-bromdylamine maleate are shown in Table III and included those patients who were frankly drowsy and had to discontinue the drug. One patient complained of being nervous and tense and was unable to sleep; one patient complained of gastrointestinal discomfort and two of urgency and urinary discomfort; one patient complained of muscular pains or aching of the legs. There were twenty-three patients who, on close questioning, stated they had a suggestive drowsiness, that these symptoms were not disturbing, that they appreciated a favorable response to the drug, and the drug did not interfere with their usual activities.

In the consideration of distribution of ages, the largest number of patients were in the first decade, numbering forty-six, and there was

reasonably comparable distribution of ages in the second, third, fourth and fifth decade, as evidenced by seventeen patients in the second, twenty-three in the third, sixteen in the fourth and nineteen in the fifth. The smallest patient distribution was in the seventh and eighth decades

TABLE IV. LENGTH OF TIME IN DAYS PATIENTS RECEIVED DIMETANE®

Days of Therapy	Number of Patients
1	3
5	15
14	40
30	28
60	21
90	11
120	10
150	11
250	1

where there were four patients in the seventh decade and three in the eighth. The youngest patient treated in the whole series was eighteen months.

The distribution according to sex was fifty-nine males and eighty-one females.

Table IV shows the distribution of patients according to days of therapy, and there were forty patients who were treated for a period of fourteen days; twenty-eight patients treated for one month; twenty-one patients treated for two months; eleven patients on therapy for five months. There was one patient who received this drug for a period of 250 days, or approximately eight months plus, and who is still on therapy.

Table V shows a comparison of daily dosages and dosage forms. There were eighty patients who were tried with dosages varying from 8 to 32 mgs per day. In the largest group of patients, sixty-nine received 16 mgs daily or 4 mgs four times a day. There were thirty-eight patients who were placed on Dimetane® Extentabs in dosages varying from 12 to 72 mgs per day. Of this group there was only one patient who received in excess of 36 mgs per day. This patient reported no significant side reactions. The patient had an angioneurotic edema involving the pharynx and did show a response to the drug. Twenty-two of these patients received one 12 mg Extentab morning and night, and thirteen patients required 12 mgs every eight hours for adequate control of symptoms. There were twenty-seven patients not previously mentioned who received 12 mg Extentabs. This group of twenty-seven patients had been previously treated with the 4 mg tablets and were changed over to the 12 mg Extentabs. Fifteen patients were given 12 mgs every twelve hours and ten patients were given the 12 mg Extentabs every eight hours.

Of the twenty-three patients placed on the elixir, seven were given one teaspoonful or 2 mgs three times a day and at bedtime, and there

TABLE V. NUMBER OF PATIENTS RECEIVING THE VARIOUS COMPOSITION UNITS OF DIMETANE® IN MGS PER DAY

Composition	Mgs Per Day	Number of Patients	Number of Patients Given Two Different Units of Dimetane®*
4 mg tablets	8	3	
"	12	4	
"	16	69	
"	20	1	
"	24	1	
"	32	2	
12 mg extentabs	12	1	1x
"	24	22	15x
"	36	13	10x
"	12-72	1	1x
Elixir—drms 1=2 mgs	4	1	
"	6	1	
"	8	7	1x
"	12	1	
"	16	11	3x
"	24	2	

*Numerals x thus indicate patients tolerating 4 mg tablets four times a day (16 mgs) and also other designated total daily dosages given during another period of therapy.

were eleven patients who received 2 drams or 4 mgs of the elixir four times a day. There were two patients who received 24 mgs of the elixir per day—one, a child with an allergic rhinitis, aged four years, and the other, a male, aged fourteen. There were two patients who received elixir of Dimetane® for an aphthous stomatitis, and they reported that this local oral administration of the drug reduced the discomfort of the oral mucous membranes. There was one patient who had her mouth traumatized coincident with orthodontic therapy and was given the compound orally and who reported that the local discomfort was minimized. In addition to the above mentioned patients who were on the elixir, one patient was switched from this to the 4 mg tablets, one twice a day; and three patients who were receiving 16 mgs a day of the elixir were given 4 mg tablets, one four times a day, or a total of 16 mgs in tablet form.

SUMMARY AND CONCLUSIONS

1. There were 140 patients presented in this study encompassing those with major allergic manifestations as a diagnosis. There were 122 patients who showed a satisfactory response to the drug.

2. In the comparison of para-bromdylamine maleate with other antihistamines, according to the patients' statements, this drug was found superior to previous antihistaminic therapy. Seventeen patients tolerated the compound when they did not tolerate other antihistamines.

3. Only eleven patients experienced any side reactions, most frequent of which was drowsiness. Five of this group, however, could not tolerate any antihistamine.

4. This study has revealed that Dimetane® is worthy of consideration in the treatment of varied allergic manifestations. The response to

treatment is favorable and in certain instances, patients who were not able to tolerate other antihistamines tolerated Dimetane® and obtained a satisfactory response.

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OTHER THINGS ARE NOT EQUAL

Now, let us ask ourselves some more questions. Kingston, the capital of Jamaica, has a population of around 150,000, or about one-seventh the population of Baltimore. In Baltimore, not more than six cases of eclampsia occur each year but in order to make the arithmetic easier, let us say seven. On the basis of these figures, we might anticipate, *other things being equal,* that an average of one case would be seen each year in Kingston. Actually, one hospital in Kingston has sixty-five to seventy cases a year. It is glaringly apparent, accordingly, that "other things" are not equal in the two cities and that these "other things," somehow or another, must have a great deal to do with the causation of eclampsia.—*Lancet,* 1:323, 1955.

CLINICAL EVALUATION OF A NEW LONG-ACTING PREPARATION IN ALLERGIC DISORDERS

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NUMEROUS antihistaminic preparations have been used for the symptomatic relief of various allergic manifestations within the past fifteen years. Their therapeutic effectiveness, however, has been limited by the severity of the side reactions, particularly the depression of the central nervous system, with resultant drowsiness and short duration of action.

The present study was undertaken as a clinical research project to evaluate the effectiveness of Sandostene Spacetabs,* a new long-acting antiallergic compound. Sandostene® is a new agent, 1-methyl-4-amino-N'-(2-thenyl)-piperidine tartrate, the chemical structure of which is quite different from most of the histamine antagonists.

Pharmacological studies by Rothlin and Cerletti[1] have demonstrated that Sandostene® exerts potent antihistaminic, anticholinergic, and antipermeability activity, as well as local anesthetic properties. In addition, it was shown to have a low degree of toxicity.

Numerous clinical studies have been published in the medical literature, the majority of these concentrating on the effect of this compound in the treatment of dermatoses, especially those of allergic etiology. The consensus of these reports[2-17] was that piperidine compound was remarkably effective in relieving the pruritus associated with these skin conditions and that this was followed in a number of cases by improvement of the dermatitis. Attention was invariably drawn to the good toleration of the compound.

More recently, Gottlieb and Yanoff[18] reported their experience with Sandostene.® They observed a high degree of effectiveness in the treatment of hay fever and found it superior to tripelennamine in cases of combined asthma and allergic rhinitis, as well as in chronic urticaria.

MATERIAL AND METHOD

Sandostene® Spacetabs were administered to 185 patients drawn from clinic and private practice. The patients comprised sixty-three males and 122 females, ranging in age from nine months to seventy-two years. They were observed over a three-month period, including the grass hay fever season, and were seen at least once weekly. Many of the subjects had more than one allergic complaint. The duration of symptoms varied from four days to forty-five years.

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*A product of Sandoz Pharmaceuticals.

Each patient was instructed to take one tablet in the morning and one in the evening. The dose was adjusted where necessary according to therapeutic response, and in children, according to age.

Every patient received a card on which to record daily observations as to the number of tablets necessary to control symptoms, the time for onset of relief, and the duration of effect. Every patient was also asked to record the severity of symptoms and the degree of relief daily as either nil, slight, moderate, or marked, as well as any side effects experienced. These reports of the subjective responses of each patient were transcribed to a special form on which all objective findings were recorded as well. Whenever possible, the therapeutic effect of the tablets was compared with the effect of other antihistaminic compounds in the same patient and recorded as better than, worse than, or equal to the other preparation.

Each patient had a complete allergic survey which consisted of a detailed history and physical examination. Complete blood count and urinalysis were performed on a random number of patients before the onset of treatment and four to six weeks later. Nasal smears and nasal and ophthalmic tests were included when necessary. The patients were permitted to continue with any previous type of anti-allergic management which included specific hyposensitization and the use of palliative measures.

The tablets were given to those patients who failed to obtain adequate relief with specific hyposensitization. The tablets were also given to those patients who could not tolerate other antihistaminic preparations because of undesirable side effects. The tablets were frequently substituted for the corticosteroids because of the well-known hazards associated with their prolonged use. New patients who presented symptoms received the tablets and injections of buffered saline, in lieu of specific hyposensitization, which they had undergone in previous years.

At the outset of the study, placebo tablets of the same shape and appearance as Sandostene® Spacetabs were employed as a control to rule out psychological factors. These were substituted for the active agent in thirty patients without their knowledge. As a test for toxicity, forty allergic patients were selected who were asymptomatic at the time and to whom one Sandostene® Spacetab was given morning and night for seven days. It was felt that any side reactions would be well demonstrated in such cases and that these candidates offered a more critical test of the agent being evaluated as regards incidence and degree of side reactions.

RESULTS

The results are summarized in Table I.

An analysis of the results showed that 150 of the 185 patients, or 81 per cent, benefited from the compound. Marked relief of symptoms was obtained by 63.2 per cent of all patients, and this was considered

TABLE I. CLINICAL EFFECTIVENESS OF SANDOSTENE® SPACETABS

Condition	Number of Patients	Excellent	Satisfactory	Unsatisfactory
Perennial hay fever	51	37	6	8
Seasonal hay fever	45	34	4	7
Bronchial asthma	29	14	5	10
Atopic dermatitis	19	10	5	4
Urticaria and angioneurotic edema	11	5	3	3
Migraine	3	2	0	1
Poison ivy	4	3	1	0
Vernal and allergic conjunctivitis	5	2	2	1
Nasal polyposis	8	5	3	0
Neurodermatitis	6	4	1	1
Contact dermatitis	3	1	2	0
Herpes zoster	1	0	1	0
Total	185	117	33	35

an excellent result. Unsatisfactory relief of symptoms occurred in only 19 per cent. Study of the records of these patients who were not relieved revealed that they had used the "antihistaminics" with similar results.

Since some of these patients presented more than one symptom, 244 separate allergic manifestations were recorded. It was interesting to note that relief of one symptom apparently invoked an improved milieu in many of these patients, which resulted in subsidence of other associated symptoms.

The therapeutic response to the tablets was reported as occurring within at least thirty minutes. The degree and duration of relief varied somewhat from patient to patient but was fairly consistent in the same patient. The charts revealed that the effect lasted from eight to twelve hours and appeared to be quite uniform throughout this period.

In the control group of forty allergic patients who were asymptomatic and received the tablets, five complained of drowsiness and two patients had dryness of the month. Only two of the thirty patients receiving the placebo tablet obtained relief. We were forced to curtail the use of the placebo when the marked relief provided by the active agent became evident early in the study. We felt that we could not withhold this from patients who were obviously in distress.

A breakdown of our observation reveals that the seasonal and perennial hay fever groups responded especially well to the compound. In both groups, comprising ninety-six patients, eighty-one (84.4 per cent) obtained satisfactory to excellent results. The antipruritic effect was particularly helpful to those patients with marked itching of the eyes, ears, nose and roof of the mouth. Prior to treatment, a number of patients with unbearable itching of the palate described this as so uncomfortable as to elicit an insatiable desire to dig at the roof of the mouth with a fork or pointed instrument. Relief from this distressing symptom was almost complete. Rhinorrhea and sneezing were modified, as was the nasal blockage to a lesser extent. Another patient's descrip-

tion of the relief obtained from the rhinorrhea was comparable to that of a suction apparatus attached to the nose and completely clearing it of all secretions. Interestingly, the sense of smell returned in a number of patients. Many patients reported they were able to dispense with their atomizers, sprays, and other ancillary medication. The tablets provided more definitive relief than other antihistaminic drugs. Furthermore, they helped to potentiate the value of specific allergic management in such cases.

Of the twenty-nine patients with bronchial asthma, nineteen (65.5 per cent) were favorably influenced regardless of the etiology. The tablets provided freedom from the dyspnea and wheezing respirations. The sustained effect obtained with one tablet before bedtime was especially dramatic in these cases. They remarked that they were freed from the usual night horror of the choking cough, gasping for breath, and the frantic search for the nebulizer. A number of patients who had previously been treated with the corticosteroids, had to discontinue them because of unfavorable reactions or the possibility of toxic effects associated with their long-term use. They found the tablets a welcome and effective replacement. The patients with chronic severe bronchial asthma did not respond as well. However, a number of these patients obtained gratifying relief of the associated nasal symptoms. The use of the tablets is indicated as an adjunct to prophylaxis in such cases.

The antipruritic activity of the tablets was quite evident in the various allergic dermatoses, including atopic and contact dermatitis, urticaria and angioneurotic edema and poison ivy as well as in neurodermatitis. The relief from the intractable itching which is usually a key problem in the management of these cases was quite noteworthy. This tended to break the vicious itch-scratch cycle. The subjective response correlated with objective improvement, as indicated by subsidence of the inflammation, involution of the skin lesions, and clearing of the secondary infection. Topical application of various lotions and ointments was obviated in most cases. Of note was a nine-month old infant with atopic dermatitis who had not had a full night's sleep since birth. She presented a papulovesicular crusted eruption, with evidence of marked pruritus as seen by the secondary infection with superimposed impetiginous lesions—the result of trauma from scratching. Marked relief was obtained with one-quarter tablet, two to four times daily. The itching and scratching were reduced to a minimum, the inflammation subsided, the skin lesions involuted, and the secondary infection disappeared. This was followed by a restful night's sleep for the first time and continued improvement thereafter.

Acute urticaria responded well, the relief from the intense pruritus being prompt with the urticarial wheals and the erythema subsiding fairly rapidly. Two patients with severe angioneurotic edema failed to obtain adequate relief. The patients with poison ivy, vernal and allergic con-

junctivitis, contact dermatitis and neurodermatitis reported satisfactory to excellent relief of their itching. Exudation was definitely reduced. The severe itching of the eyes and the photophobia in the patients with vernal conjunctivitis was markedly relieved in two cases and moderately in another two. The tenacious "chewing-gum" discharge decreased in amount.

TABLE II.
INCIDENCE AND DEGREE OF SIDE EFFECTS

Types	Number	Slight	Moderate to Severe
Drowsiness	24	19	5
Dryness of mouth	12	10	2
Constipation	2	2	—
Nausea	3	3	—
Dizziness	1	1	—
Total	42	35	7

All eight patients with nasal polyposis and associated allergic disturbances exhibited satisfactory to excellent relief. Four of the patients had multiple polypectomies with recurrences of the polyps. The subjective relief did not correlate with objective findings in all of the patients. We realize that patients with nasal polyposis and multiple polypectomies over a period of thirty years or more will not manifest a sustained objective response in a few months. The subjective response to the piperidine compound, however, was quite dramatic, and indicated that adequate control of symptoms could be obtained in this group of patients.

Of interest was one patient with herpes zoster referred to this department because of severe intractable post-herpetic pain of one year's duration. Various types of therapy had been instituted previously without relief. The chest was exquisitely sensitive and an attempt at palpation was resisted. The pain was severe and continuous, and the patient had difficulty in finding a position to sleep. After treatment with one tablet, morning and night for four weeks, the patient has shown remarkable improvement through a decided reduction of pain.

SIDE EFFECTS

Forty-two patients in this series reported side effects. However, the majority of these were so slight and transient that they constituted no problem, many subsiding completely as the patient continued with the medication. This was especially true of drowsiness, with only five cases finding this a limiting factor to continued treatment. Dryness of the mouth, which must be related to the anticholinergic activity of the compound, was sufficiently disturbing to warrant discontinuation of therapy in only two cases. Urinalyses and blood studies were conducted initially and again four to six weeks after institution of therapy in sixty-two patients selected at random. These were all within normal limits.

As another facet of this study, we reviewed our records in seventy-four cases where antihistaminics had been administered previously (Table III). These patients were asked to list their preference for the various preparations they had used. Sandostene® Spacetabs were selected by fifty-eight patients who stated that they derived greater relief of their symptoms from this agent than from the other drugs tested. One of

TABLE III. EFFECTIVENESS OF SANDOSTENE® SPACETABS COMPARED WITH OTHER ANTIHISTAMINICS

Sandostene® Spacetabs	Number
Better than other antihistaminics	58
Worse than other antihistaminics	7
Same as other antihistaminics	9
Total	74

six different antihistaminics was indicated by seven patients, while nine patients could detect no difference.

DISCUSSION

The treatment of allergic disorders starts logically with an attempt to determine the nature of the specific allergen, then to remove or avoid the sensitizing factors, and, if this fails, to institute hyposensitization. Admittedly, this plan represents an oversimplification of the problem and may fall short of the mark, so that symptomatic therapy has to be resorted to. The latter also is often necessary to provide relief of troublesome symptoms which may occur during the course of hyposensitization.

The advent of the antihistaminic drugs has proved to be a welcome boon as adjunct therapy in the treatment of allergic disorders. While one might think that a plethora of these agents clutter up our therapeutic armamentarium, experience has shown that this variety serves a useful purpose since there is a wide difference in individual response and elicitation of side effects.

This suggests that the ideal agent would be one having a high degree of effectiveness and one well tolerated by the greatest number of patients. The results obtained in this study indicate that piperidine compound comes closer to this goal than other preparations we have employed to date. Review of our results in an unselected group of patients reveals that these were of benefit in 81 per cent of all patients in this series, and that troublesome side effects were experienced by only seven patients in this series. The side effects graded as slight were usually of short duration and did not constitute a problem. As a matter of fact, the mild sedative effect exerted may well have contributed to its therapeutic value, especially in those cases where itching was a problem.

There is no denying the fact that this wide therapeutic index increased the clinical usefulness of the tablets. One can speculate that the reduction in cellular permeability attributed to this drug may be more important than actual histamine antagonism. This contention is supported by the fact that the compound is equally effective in allergies of the mucous membranes of the nose, eyes, and respiratory tract as it has been shown to be in allergic manifestations of the skin. Clinical evidence to support this view is derived from the excellent results obtained in cases of perennial and seasonal hay fever as well as the encouraging results in cases of bronchial asthma.

The sustained action of the tablets, ranging from eight to twelve hours, has great practical significance in that it necessitates the use of only two tablets per day to provide effective and consistent relief. This was especially valuable in suppressing nocturnal symptoms which are known to be more frequently distressing than those occurring during the day. Clinical effect usually was manifested within fifteen to thirty minutes after ingestion of the tablet.

Initially, placebo tablets were substituted for the Sandostene® Spacetabs in thirty patients. It was our intention to test the placebo and the active agent alternately in all patients without their knowledge. However, the marked difference in effect observed by the patients receiving both forms defeated this purpose. We recognize the need for control and realize that there are many factors beyond the use of placebos that can affect a drug evaluation. We agree with Lasagna[19] that the most satisfactory analysis of a new drug is obtained when it is tested carefully by a variety of independent observers in different clinics with differing types of patients under dissimilar conditions. It is our hope that this study will contribute to this goal and to the final appraisal of the compound.

SUMMARY

A clinical evaluation of Sandostene® Spacetabs in 185 patients is presented. Its effectiveness in the treatment of a variety of allergic disorders benefited 81 per cent of the patients in this series. The low incidence of side effects contributed greatly to its clinical usefulness.

Therapeutic effect was obtained within thirty minutes of administration and persisted for periods of eight to twelve hours. This sustained activity represents an important attribute of this agent and has decided practical value in the management of such cases.

Subjective and objective evidence supported the patients' preference for Sandostene® over antihistamines previously employed. This was based on a greater therapeutic effect and better toleration. It was especially valuable in cases unable to tolerate the corticosteroids or where continuation of this form of therapy presented a hazard to the patient.

CONCLUSION

Sandostene® is not a curative agent nor does it replace specific allergic therapy. The proper management of allergies calls for the removal of the offending allergen from the diet or environment following an etiological diagnosis. If this is not possible, specific hyposensitization is indicated. When these measures fail, other methods must be employed. On the basis of our experience with the Spacetab, we consider Sandostene® to be the most effective agent presently available for symptomatic treatment of allergic disorders.

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ANAPHYLAXIS AND THE NERVOUS SYSTEM

Part II

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IN A PREVIOUS report,[1] we showed that lethal anaphylactic shock can be prevented by bilateral focal lesions in the tuberal region of the hypothalamus, carried out by the Horsley-Clarke stereotaxic technique. Our next aim was to determine whether the inhibition of the shock phenomenon could be produced only by lesions of the tuberal region or also by lesions

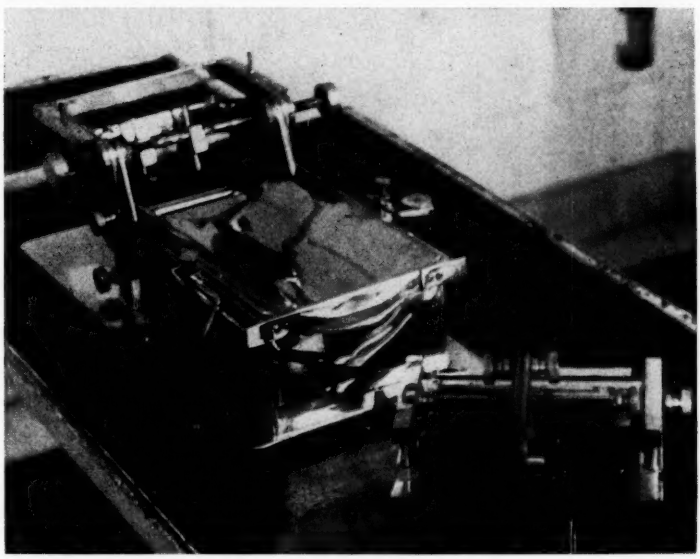

Fig. 1. Stereotaxic technique. The larger instrument is used for fixation of either guinea pigs or rabbits (see Figs. 3 and 4). The smaller instrument consists of three vernier scales to determine exact spatial localization of the electrode which is attached.

in other regions of the hypothalamus and elsewhere in the central nervous system. Furthermore, we wished to decide whether the anti-anaphylactic effect of tuberal lesion also manifests itself in local anaphylaxis and generally in cases of allergic inflammation.

MATERIALS AND METHODS

Focal electrolytic lesions of the hypothalamus or other areas of the nervous system were produced by means of the stereotaxic technique (Figs. 1-4). Details of the technique used are outlined in our first report.[1]

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Operations were performed under ether anesthesia. After the operation, the animals received ample subcutaneous injections of saline solution, as experience with rats taught us that the close vicinity of the pituitary to the area of operation might induce lethal diabetes insipidus. Similar experi-

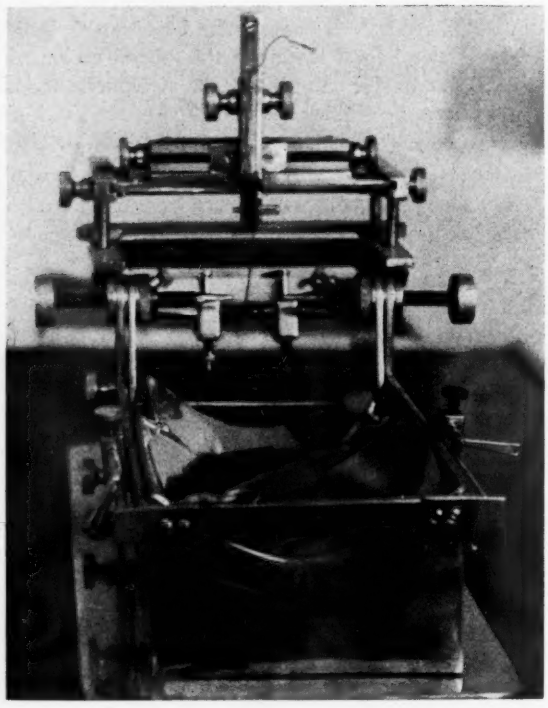

Fig. 2. The Horsley-Clarke stereotaxic apparatus, modified by Szentagotai.

ences made us keep the animals in an environment of 25-26°C for the next few days. Though measurements of heat regulation were not made in the present series of tests, we have learned to reckon with disturbances in the heat regulating system. In spite of these precautions, postoperative lethality in rats and guinea pigs was about 50 per cent. Most of the animals died within twenty-four to forty-eight hours. Animals which survived this period showed rapid improvement in their general condition. In fact, they can be said to have regained their preoperative fitness in three to four days. By that time, both appetite and vitality of the guinea pigs were restored. The few animals which died after forty-eight hours either fell victim to cerebral abscesses bordering on the operative perforation channel or starved as a result of blindness caused by injury to the optical tract and a probable concomitant anosmia.

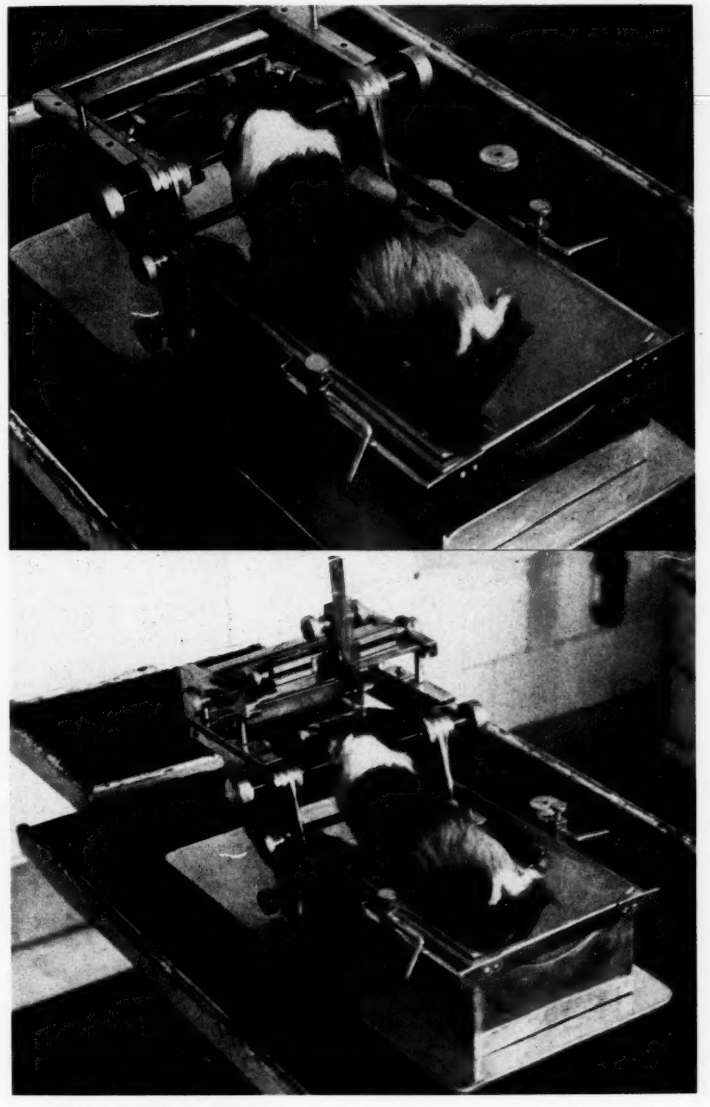

Fig. 3. *(above)* The animal's head is immobilized by introducing conic screws into its external auditory canals and fixing his incisors on a gliding bridge. The animal's head is then depressed by steel springs in order to maintain contact between the incisors and the gliding bridge.

Fig. 4. *(below)* The electrolytic focal lesion itself is made by the anode attached to a unipolar needle electrode protected to its tip by glass casing. The cathode is attached to an indifferent electrode. The duration of electrolysis is eight seconds at two or three milliamperes. The skull is trephined with an electric dental drill using a spheric bit.

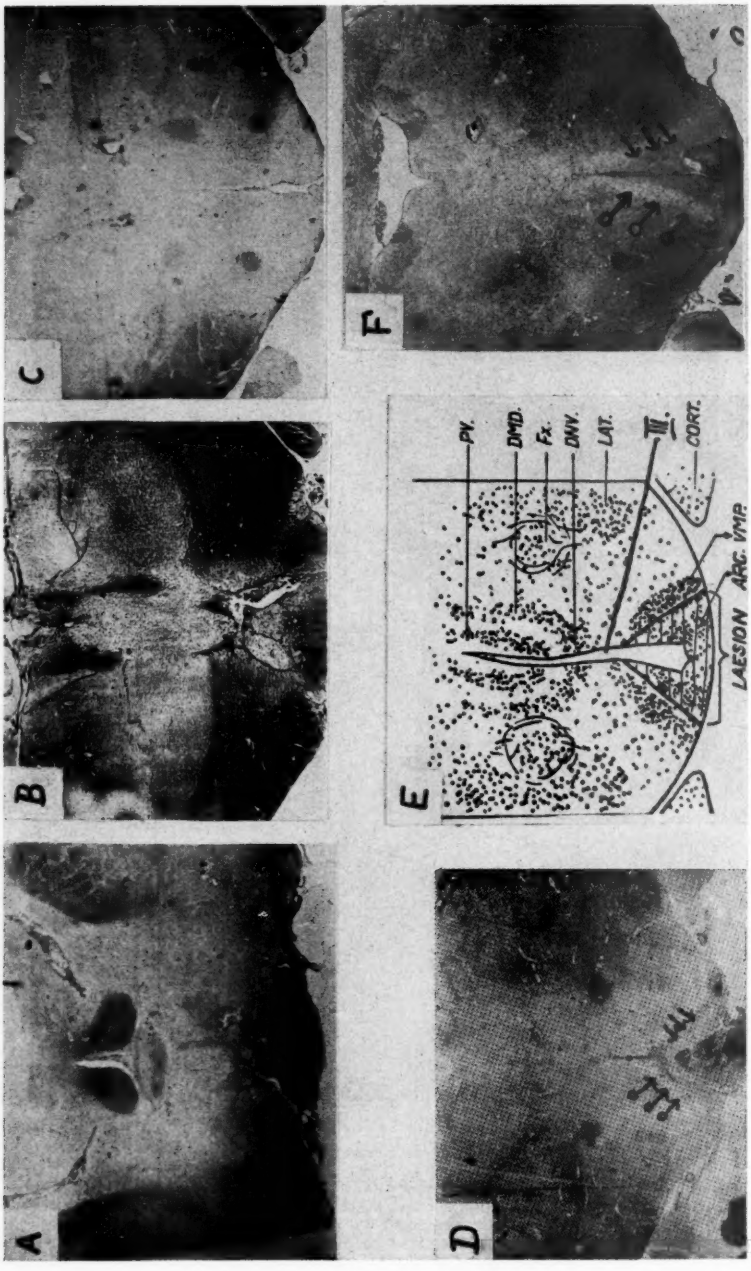

Fig. 5. (See legend on opposite page.)

I. The Effect of Focal Lesions in the Central Nervous System on Anaphylactic Shock in the Guinea Pig

Our experiments were carried out on 664 guinea pigs, male and female, weight 300-400 g. We sensitized the animals by one subcutaneous injection of 0.2 to 0.3 ml of undiluted horse serum and carried out the operation mentioned above on the seventh or eighth day after sensitization. Shock was provoked by intravenous reinjection of 0.5 to 1.0 ml of undiluted horse serum thirteen to fourteen days after operation and twenty to twenty-one days after sensitization.

The localization of the lesions was checked after the death of the animals (or sacrifice of the survivors using carbon monoxide), first macroscopically under the stereoscopic microscope, then by histologic examination. In each case we made approximately fifty serial sections from the brain region in the frontal-occipital direction. Typical lesions are exemplified in Figure 5.

The 664 guinea pigs at our disposal were put in six groups on the basis of the histologic localization of the lesion:

First group.—This group contained 147 animals in whom the tuberal injury was made seven or eight days after sensitization (using the standard procedure outlined above) and also sixty-eight additional animals in whom the tuberal injury was made seven or eight days before the first injection of antigen. Since no significant differences were noted in the results obtained with these two procedures, all 215 animals are listed together.

Second group.—In this (sham operative) group were classed forty-eight guinea pigs. The electrodes were inserted in the tuberal region without, however, applying electrolysis. Thus, all the stereotaxic operational techniques in all their usual phases were applied, with the exception of electrolysis. As the later histologic examinations showed, only the trepan bore was visible, but no focal lesion.

Third group.—This group contained fifty-eight guinea pigs with lesions in the supraoptical region of the hypothalamus.

Fig. 5. Typical lesions. *A.* The lesion invades the frontal level of the tuberal region where it reaches n. ventromedialis. It lies mainly in the posterior level of the supraoptical reigon. *B.* A confluent bilateral lesion in the middle zone of the mammillary region. *C.* Small, bilateral, extrahypothalamic lesions in the ventral, nuclear group of the thalamus. *D.* A midline lesion on the infundibular region of the tuber cinereum extending to the base of the brain (simple arrow indicates colliquative zone, arrow with circle indicates zone of vital reaction). *E.* Schematic drawing illustrating the sites of the lesions in the middle zone of the tuber cinereum (Krieg). PV—Tractus periventricularis. DMD—Nucl. dorsomed. pars dorsalis. DMV—Nucl. dorsomed. pars ventralis. LAT—Nucl. lateralis hypothalami. ARC—Nucl. arcuatus. VMP—Nucl. ventromed. pars post. FX—Columna fornicis. III—Ventr. cerebri III. CORT—Temporal lobe. *F.* A confluent bilateral lesion in the middle of the tuber cinereum extending to the base of the brain.

Fourth group.—In this group we had fifty-one guinea pigs with lesions in the mammillary region of the hypothalamus.

Fifth group.—This group contained forty-two guinea pigs where the lesions were located outside of the hypothalamus, in cortical, thalamic, mesencephalic, et cetera, regions.

TABLE I.

Place of Lesion	Number of Animals	Lethal Shock	Severe Shock	Mild Shock	Without Reaction
Tuberal region	215	28	34	39	114
Sham operations in the tuberal region	48	46	2	—	—
Supra-optical region	58	40	6	10	2
Extrahypothalamic region (cortex, thalamus, mesencephalon)	42	39	3	—	—
Mammillary region	51	48	2	—	1
Control group	250	217	19	9	5

TABLE II.

Place of Lesion	Number of Animals	Lethal Shock	Severe Shock	Mild Shock or Without Reaction
Tuberal region	215 (100%)	28 (13%)	34 (16%)	153 (71%)
Other regions	151 (100%)	127 (84%)	11 (7%)	13 (9%)
Control group	298 (100%)	263 (89%)	21 (7%)	14 (4%)

Sixth group.—This group consisted of 250 control guinea pigs on which no operation had been performed. Sensitization and provocation of shock were completely identical with the operated groups.

Results of the experiments are shown in Table I.

The first vertical column in Table I shows the histologically confirmed location of the lesion and the second vertical column the number of animals in the group. Columns 3, 4, 5 and 6 show the number of animals which, after challenge, died or were gravely or mildly shocked, or remained completely without reaction.

The data show that in the case of tuberal lesion approximately 71 per cent of the animals are protected against shock, while in cases of supra-optical, mammillary and extrahypothalamic lesions, reactivity is not significantly different from that of the controls.

This spatial specificity becomes still more evident in Table II. This table shows the distribution somewhat differently: (1) the animals reacting with a mild shock and with no shock have been combined, and (2) the distribution of all other kinds of lesions appears in one group. As contrasted with the protection of 71 per cent in case of tuberal lesions, in the other areas it is only 9 per cent.

Thus, the anti-anaphylactic effect described in Reference 1 appears to be specifically connected with lesions of the tuberal region, strictly circum-

scribed within the hypothalamus. In cases of extrahypothalamic lesions, anti-anaphylactic effects cannot be produced at all. It should be mentioned that simple stabbing of the critical area (regio tuberalis), without electrolysis, does not have anti-anaphylactic effect. In order to achieve protection, the area in question must be destroyed.

II. The Effect of Tuberal Lesion of the Hypothalamus on the Arthus Phenomenon in the Rabbit, and on the Sanarelli-Shwartzman Phenomenon and on Artificial Turpentine Eczema in the Guinea Pig.

It seemed to be worth while to examine whether tuberal lesions inhibit reactivity in local manifestations as well as in generalized anaphylaxis.

For this purpose, we used three well known models, each of them easy to evaluate but based on different principles, namely: (1) Arthus phenomenon, (2) the turpentine eczema, and (3) the Sanarelli-Shwartzman phenomenon. The first two represent experimental models different not only because the character of the first one is vasculo-epithelial while that of the second one is an epithelial hypersensitivity, but also because we may assume that the two different skin manifestations are connected with two different types of antibodies.[2]

Inclusion of the Sanarelli-Shwartzman phenomenon permitted us to study the effect of tuberal lesion on a phenomenon which is connected with a change in the general reactivity of the organism, but which, at the present state of our knowledge, cannot be considered as allergic.

First group.—The effect of tuberal lesion on the Arthus phenomenon was studied in rabbits, the classic object of experimentation for the Arthus phenomenon.

We sensitized fourteen rabbits (weight 2.5 to 3 kg) with undiluted normal horse serum, given subcutaneously in the abdomen in quantities of 3, 4, 5 and 6 ml at four-day intervals. Tuberal lesions were produced in eight rabbits on the fourteenth day following the last sensitization. Six rabbits served as controls. In both groups, we reinjected 1.0 ml homologous antigen on the seventeenth day following the last sensitization beneath the shaven skin of the abdomen. Three days after the reinjections, there was no significant difference in intensity of reaction between the tuberal-injured and the control animals. Thus we conclude that tuberal lesion does not interfere with the development of the Arthus phenomenon.

Second group.—We examined the effect of tuberal lesion on artificial turpentine eczema in the guinea pig in two experimental groups. The two groups differed only in that we began the turpentine treatment in group (a) one day after tuberal lesion, and in group (b) fourteen days after tuberal lesion. In group (a) we used five tuberal-injured and five control guinea pigs, and in group (b) fourteen tuberal-injured and eleven control guinea pigs.

During a period of ten days we brushed an area of approximately 1 to 1.5 cm diameter in the middle of the shaven skin of the abdomen of both the tuberal-injured and the control animals with a 50 per cent turpentine solution. To prevent the solution from spreading, we surrounded the site of treatment with a wall of vaseline. After applying turpentine for ten minutes, the solution was removed with cotton saturated with benzine.

After the fifth or sixth treatment with turpentine, the tuberal-injured and the control animals became greatly irritated; they scratched their abdomens all the time. In this phase, the initial hyperemic stage of eczema appeared in the treated sites of some of both the tuberal-injured and the control animals. These symptoms became more outspoken with the subsequent brushings. After the eighth, ninth and tenth treatments with turpentine, both the tuberal-injured and the control animals developed the typical symptoms of eczema.

In order to decide whether generalized hypersensitivity had developed, four days after the last turpentine treatment one drop of a 1 per cent turpentine solution was placed on a small shaven area of skin on the right hind leg of both the tuberal-injured and control animals. After application of this test, both the tuberal-injured and the control animals soon became restless, scratching and licking the turpentine-treated sites. A few hours later, all the animals showed hyperemic and edematous inflammation of the test sites. On the basis of these observations, it appears that the development of turpentine eczema is not influenced by tuberal lesion.

Third group.—In this group, we examined the effect of tuberal lesion on Sanarelli-Shwartzman phenomenon. The preparation of the animals in group (a) was begun twenty-four hours after producing tuberal lesion, and in group (b) seven days after production of tuberal lesion.

Group (a).—We made intracutaneous injections into the shaven skin of the abdomen of ten tuberal-injured and five control guinea pigs with 0.5 ml filtrate of *B. coli.* Twenty-four hours after the preparatory injection we reinjected 0.6 ml of the filtrate into the jugular vein. Readings of the result were made forty-eight hours after the reinjection. In the area of the preparatory inoculation, both the tuberal-injured and control animals developed the hemorrhagic inflammation characteristic of the Sanarelli-Shwartzman phenomenon.

Group (b).—On seventeen tuberal-injured and fifteen control guinea pigs, we produced the Sanarelli-Shwartzman phenomenon in the same way as in Group (a). The Sanarelli-Shwartzman phenomenon developed in both groups of animals within forty-eight hours following the reinjections.

Except for some restlessness, we did not observe general symptoms in either group.

CONCLUSIONS

1. In the majority of cases, focal lesion of the tuberal region of the hypothalamus of the guinea pig produces protection against anaphylactic shock. The anti-anaphylactic effect of tuberal lesion is the same whether the operation precedes or follows sensitization.

2. Lesions produced by simple stabbing of the tuberal region of the hypothalamus do not influence the development of anaphylactic shock.

3. When other regions of the hypothalamus or such other regions of the central nervous system as we have listed have been injured, the protection is diminished or disappears proportionally to the distance from the tuberal region.

4. Thus it appears that the anti-anaphylactic effect of our intervention is specifically related to the electrolytic destruction of the tuberal region.

5. Tuberal lesion does not prevent the development of the Arthus and the Sanarelli-Shwartzman phenomenon nor that of experimentally-produced turpentine eczema.

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Submitted February 13, 1957

SCIENCE THROUGH UNION

But with the growth of science the task has become more formidable. For example, *Chemical Abstracts,* which covers the world literature in chemistry, abstracts about 100,000 articles per year from about 7,500 journals, 2,000 books, and the patents of twenty-two countries. The future holds no hope for a diminution of effort. The rate of publication in chemistry has doubled every eight and one-half years during this century and there is no sign of leveling off yet. The volume of publication is increasing in other branches of science, too. The total job to be done can be appreciated by considering that some 50,000 scientific journals currently publish about two million articles per year.

This is clearly the time for a reappraisal of our methods for handling scientific information.—*Science,* 127:3294.

EXTRA-RESPIRATORY TRACT SYMPTOMS OF POLLINOSIS

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THE CLASSIC symptoms of hay fever have frequently been discussed. The patient's history alone is so typical that a diagnosis of hay fever can often be made with no corroborative skin tests. But other symptoms are present which are often ignored. This applies especially to such patients as may be reactive to pollen and yet present none of the classic symptoms of hay fever. These patients deserve special consideration with respect to treatment.

The purpose of this paper is to point out the often-ignored symptoms of pollinosis, particularly those which might be referred to as extra-respiratory. Of these the psychologic and neurologic manifestations of pollinosis will be emphasized.

A study was made of three hundred adults who clinically reacted to pollens. The psychologic and neurologic symptoms which they experienced were tabulated. Although it was difficult to evaluate the symptoms within a tight statistical pattern because the personalities of individuals varied so greatly, the following tabulations could be made from the patient's answers to questionnaires.

Of the three hundred, 285 showed personality changes. These consisted of either one or all the symptoms of irritability, jumpiness and jitteriness, inability to concentrate, nervousness, mental depression, carelessness in dress, and poor judgment. Two hundred and four presented evidence of fatigability, 174 sleeplessness, and seventy-five headache.

Twenty-two children under the age of ten suffering from hay fever were studied separately and, of this group, eighteen showed fatigue, difficulty in "standing still," chorea-like symptoms, fretfulness, irritability and temper.

For comparison, 300 adult asthmatic patients who did not clinically react to pollens were also studied. Of these, 191 showed personality changes including irritability, jitteriness and jumpiness, inability to concentrate, nervousness, carelessness in dress and poor judgment. Two hundred and sixty-two gave evidence of fatigue, 204 sleeplessness, 102 headache, and twenty-seven fever.

Of the adult allergic groups, the patients with pollen sensitivities presented a far greater number of extra-respiratory tract symptoms than did the asthmatic patients with no sensitivity to pollen. There were two exceptions—fatigue and sleeplessness—and this is understandable in cases of respiratory difficulty.

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No statistical pattern was established for the asthmatic child under ten years of age as compared to the child presenting hay fever.

We all recognize the fact that an overdose of pollen extract may cause such symptoms as apprehension and fear, and signs such as a rapid and weak pulse and lowered blood pressure. I am sure many of us on occasion have inadvertently given an intravenous pollen injection. This is always characterized by a severe sudden excruciating headache, which illustrates very definitely that pollens can react to cause symptoms not usually associated with typical hay fever symptoms. We should keep in mind that the same results may follow the inhalation of pollens, particularly in hypersensitive individuals.

The extra-respiratory tract symptoms are undoubtedly often ignored in pollinosis, because we think of the classic symptoms as the only important signs in the diagnosis. Yet there have been many cases in which the classic symptoms of hay fever have been at a minimum, and the extra-respiratory tract symptoms have been the most pronounced and troublesome as far as the patient was concerned. The following patient is an outstanding example:

A physician, aged sixty-one, noticed for a number of years that, beginning in February and reaching a peak in March, he became exhausted easily and required eight to ten hours sleep. He was irritable with his office personnel, unable to concentrate, and had marked mental depression. He presented a fine tremor and thus was unable to perform his surgical duties as an otolaryngologist.

These symptoms were noted as well by his wife, colleagues, and employes. He concluded they were due to hard work and exhaustion, reaching a climax at that time of year. He would go to Palm Springs, where he recovered almost immediately. After a month at Palm Springs, he would return home to lead a normal life.

Physical examinations made by competent internists proved no disease to be present and a diagnosis of "nervous exhaustion" was made.

The patient's own observations led him to suspect tree pollens, because his symptoms always became evident during the tree pollination season. He was skin tested and found markedly sensitive to the pollens of cottonwood, hazel and willow. He presented none of the classic signs or symptoms of hay fever, no sneezing, no nasal congestion or discharge. The color of the nasal mucous membrane was normal. The only abnormalities present were those listed above.

For the next four years he was given a course of tree pollen injections. He reached a top dose of 0.40 mg total nitrogen per cubic centimeter of tree pollen, and during this period of time had no discomfort and felt entirely normal. On one occasion he had a constitutional reaction and presented symptoms of headache, fatigue and weakness, persisting for twenty-four hours. Thereafter his dose was kept below the level which was followed by the reaction.

During the following year (with pollen treatment), he remained symptom-free.

There have been many other instances of extra-respiratory symptoms of pollinosis reported. Rowe[1] observed three cases of seasonal headaches occurring during the pollen season, two of which were relieved by pollen desensitization. Cohen and Janjigian[2] reported epileptic seizures in patients

exposed to pollens. Rowe[3] also noted a child with severe epilepsy appearing in the summer, due to hypersensitivity to pollens. Cooke[4] reported headaches in a hay fever patient twenty-four hours after each pollen injection. May[5] observed somnolence in August in a pollen-sensitive patient who did not present the classic symptoms of hay fever.

Sternberg,[6] in 1942, described a patient who complained, for eleven years, of incapacity at the end of August and during the first few weeks of September. He became drowsy, listless, unable to concentrate. His thoughts were confused and he slept most of the time. His blood pressure was low. He had no symptoms of hay fever or asthma and no other classic symptoms of allergy were present. Skin tests with ragweed pollen showed marked reactions. He was treated with injections of ragweed pollen extract and was completely relieved of symptoms except when overdosed. Sternberg suggested that the pathology might lie in an allergic reaction of a hyperemic or edematous type in the tissues of the nervous system.

In studying the pollen reactions in children, Kahn[7] observed psychic changes. He noted mental deficiency and listlessness alternating with spells of intense temper and fury. These children were extremely cross and irritable, resisted all handling and cried at the slightest provocation. He further stated within a few weeks after pollen treatment was instituted that the entire picture changed. He attributed this to pollen toxemia.

Other vaguely defined neurologic and psychologic symptoms have been reported in literature.

Not only may these occur but also eczematous lesions from the inhalation of pollens have been reported. While the total number of case reports may be small, allergists do see these cases from time to time.

A most unusual skin manifestation was reported by Mitchell,[8] who described five cases in pre-adolescent girls with intense itching in the region of the muco-cutaneous junction of the vulva and the vagina. The symptoms occurred during the ragweed season and were relieved by injections of ragweed pollens.

While many unusual and bizarre symptoms have been reported from the inhalation of pollens, the neurologic and psychologic manifestations are being emphasized. The neurologic and psychologic symptoms are sometimes so common and taken for granted by the patient as part of the symptom complex that they are ignored. In a few instances, as reported here, they sometimes outweigh the classical picture of pollinosis.

When doing a routine series of skin tests a patient is discovered to be reactive to pollens in the absence of symptoms of hay fever, further questioning will bring to light the extra-respiratory symptoms which have been overlooked or ignored.

The question arises as to whether one is justified in treating this type of patient. I wish to emphasize that if some of the extra-respiratory

tract symptoms are present and the patient is pollen-sensitive one is justified in pollen desensitization.

What produces these symptoms is open to speculation. Pathologic data are lacking. No deaths have occurred during one of these allergic states. Localized edema and hyperemia of urticarial or the angioedema type are thought to be the explanation. The presence of intracranial edema might support this. Lesions as hemorrhagic, exudative, productive, necrotizing inflammations as seen in purpura and the erythema groups, eczema and the periarteritis, may exist. The fact remains that these symptoms do occur.

There is one other possibility. We speak of the threshold in allergy and that the presence of any exciting allergic agent may lower the threshold. Whatever the cause, the pollens are concerned in the etiology of the seasonal extra-respiratory symptoms.

CONCLUSIONS

1. Extra-respiratory tract symptoms of pollinosis may occur in an individual sensitive to pollens in the presence or absence of signs and symptoms of pollinosis.
2. In the absence of the classic symptoms, one should be keenly observant of these extra-respiratory tract symptoms of pollinosis.
3. These patients need pollen desensitization as much as do those presenting the classic symptoms.
4. One must be just as cautious with pollen therapy in these patients as one would be in those in whom the classic symptoms were present.

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Medical Arts Building

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DERMATITIS OF THE NOSE DUE TO SNIFF TOBACCO

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ACCORDING to Schwarz, Tulipan and Peck,[1] dermatitis due to tobacco is rare. In the cases reported by them, dermatitis was presumably caused by chemicals used in tobacco processing or by the fermenting process itself.

In the three cases reported by Vero and Genovese,[2] dermatitis was caused in cigar makers by recently fermented tobacco. The authors state that "no case of dermatitis due to either raw tobacco leaves or dry tobacco had been observed, and none was reported in smokers as due to contact with cigars."

In view of the absence of reports of dermatitis caused by finished tobacco, the following case may be of interest:

CASE REPORT

The patient, a healthy man, aged seventy-two, would sniff tobacco which he mixed with a few drops of arrack* in order to prevent sleepiness. He had sniffed tobacco for twenty to thirty years but had started to add drops of arrack only about six months previously. His friends who also sniffed tobacco did not suffer any inconveniences.

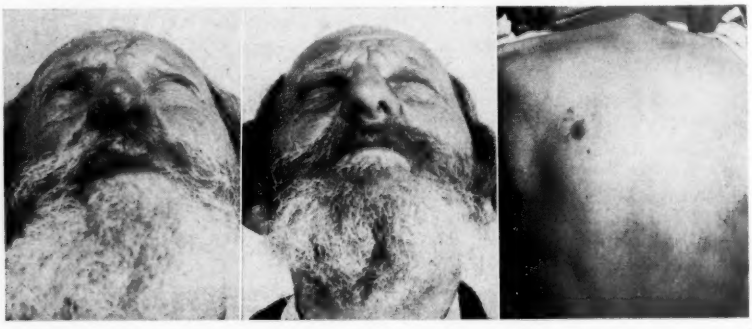

Fig. 1. (*Left*) Patient's nares on first visit. Fig. 2. (*Center*) Patient's nares after discontinuing sniff tobacco. Fig. 3. (*Right*) Patch test positive to tobacco.

On examination there were found swelling, redness and oozing in the region of the external nares (Fig. 1). Also the nasal mucosa was swollen and red. Since, as determined by patch testing, arrack is a primary irritant, the patient was advised to refrain from adding arrack to his sniff tobacco. However, his dermatitis recurred

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*Arrack is alcohol distilled through aniseed. It may be prepared also by adding synthetic anethol to alcohol.

on two occasions. Hence, we may conclude that it was the tobacco and not the arrack which acted as the causative agent (Fig. 2).

Forty-eight hour patch tests with tobacco performed on the patient were positive (Fig. 3). Patch tests with arrack produced a "blister."

For control purposes, ninety-seven patients visiting the clinic because of other dermatoses (90 per cent thereof suffering from eczema) were tested with tobacco. Six of these patients reacted eczematously; ninety-one did not react. The positive patch tests were seen in patients suffering from acute eczema, and may be explained as isomorphic reactions (Koebner's phenomenon).

Since 80 per cent of the patients on whom patch tests with arrack were performed reacted with a "blister," testing with this irritant was discontinued.

Histologic examination of the "blisters" caused by the testing with arrack revealed that they were "intraepidermal"; in the patients who had shown an eczematous reaction to the testing with tobacco, spongiosis was present.

COMMENT

This case is reported in view of its rarity. A perusal of the literature including the *Excerpta Medica,* fails to disclose a precedent. That the habit of sniffing tobacco is not dying out in this country is proven by the fact that the production of sniff tobacco is increasing and, according to information from the Director of Excise Tax, has risen from 25,000 kilograms in 1953 to over 33,000 kilograms in 1955, which amounts to approximately 200 grams per capita.

SUMMARY

A case of dermatitis of the nose due to sniff tobacco is described.

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Submitted November 15, 1956

When we inquire into the cause of disease, we are often brought to consider a long chain of relative circumstances. . . . Somewhere, however, there is a particular event that is of cardinal importance to the individual since it may be said to have set the chain of events in motion in him.—Sir Thomas Lewis, Clinical Science, Illustrated by personal experiences. London: Shaw and Sons, Ltd., 1934.

ALLERGY AS A CAUSE OF GENITOURINARY SYMPTOMS

Clinical Considerations

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ALLERGY as a cause of genitourinary symptoms has been recognized and described by various workers. Several textbooks mention this briefly but rarely cite examples. It is my belief that the rank and file of physicians are not familiar with allergy as a cause of genitourinary symptoms and, hence, overlook it. In the index to the *Journal of Urology* I was able to find only four articles on allergy since 1940.[1-4] After reading another article in which allergy is mentioned, I feel certain that it should be considered much more in several of the cases reported.[5] I have discussed this problem with several urologists and only one out of three considers this possibility, although they occasionally have attributed symptoms to the acidity of certain foods. However, in biochemistry we learned that most of the fruits and vegetables they mentioned as being high in acid content are changed in the body and are eliminated as alkaline.

CASE REPORTS

Two cases are presented in which the allergic symptoms were unrecognized.

The first case is that of a seventy-four-year-old white woman who complained of soreness of the vagina for about a month. Her past history is significant in that she had frequent "kidney infections" over the past thirty to forty years. She has an almost constant watery nasal discharge with chronically red irritated nares. She has used cathartics frequently and has taken an enema almost daily for many years. While taking her history it was brought out that apples, pineapple, lemon, grapefruit, rhubarb, oranges, and tomatoes had given her a sore mouth and symptoms of cystitis. Suppositories and the use of vinegar douches had cleared the inflammation of the vault, but the vulvar irritation had become worse. Her doctor told her that perhaps pressure from her bladder or varicose veins was causing the trouble. Because of her history and the negative findings on examination, except a little reddening of the vulva, she was advised to discontinue using vinegar douches and to avoid the offending foods. Prompt improvement followed. As is the case with some older people, she will not adhere strictly to her diet and sometimes breaks over, thinking that "just this once won't hurt." She then has trouble for a day or two, as when she ate pineapple and had a little urinary burning for a day.

The second patient is a forty-three-year-old white woman who was first seen with the complaints of urgency, frequency, burning and dysuria. She had previously been treated on at least two other occasions with oral penicillin, which she stated relieved her in two to four days. Nothing is known of the urinary findings on the previous occasions, but when seen in my office there were no abnormal urinary findings. When the penicillin failed to relieve her within two days, allergy was considered. After an intravenous injection of aminophylline, which often

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relieves some allergic symptoms, she had immediate and complete relief. The next step was to discover what was causing the attacks of cystitis. It was noted that she had several meals in succession containing tomato . . . spaghetti once, and a salad containing tomato the other times. She agreed to take a specific feeding test with tomato in the office several days later. That evening following the test she had a mild attack of cystitis. She got along quite well without tomatoes until persuaded by some well-meaning friends to eat yellow tomatoes which are said to contain less acid than the red ones. She flared up after a few days with a severe attack of cystitis and was again relieved with intravenous aminophylline. Later in the season another attack followed the ingestion of peaches. Being the wife of a country minister, she was kept well supplied with peaches during the late summer. We found out that she could eat them in spaced feedings a few days apart so that she did not get a cumulative effect from them.

I was able to follow her for about a year until the family moved several hundred miles away. She had remained symptom-free simply by omitting the offending foods from her diet or spacing them far enough apart. I had a request recently from this patient for the name of the medicine used to relieve her. She stated she had been having trouble every summer, but none of the doctors she has consulted believe that her trouble is allergic in origin and will not try to find what new allergen may be causing her trouble. They do not give her aminophylline; they simply prescribe Pyridium tablets and it takes about three weeks to recover from an attack.

Both of these patients show how allergic symptoms can recur for years without being recognized. Worse yet is the attitude of the doctor in disregarding the suggestion that the trouble may be allergic, as cited in the second case.

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USE OF TERM "INFANT" IN DRUG LABELING

The regulations affecting special dietary foods (21 CFR 125.1 (d)) define an infant as a child not more than twelve months old. Apart from this, the Food and Drug Administration has not established any definition of the term "infant." Some question has arisen whether, for the purposes of drug labeling, an infant means a child up to one year of age or a child up to two years of age. Until the term is more precisely defined by legislation or formal regulation, where the exact meaning of the term is significant, manufacturers should qualify any reference to "infant" to indicate whether it refers to a child who is not more than one year of age, or a child not more than two years of age.—*Federal Register,* November 30, 1957.

ALLERGY IN SKIN DISEASES

Bacterial, Pollen and Food

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THERE are many interesting facets in the relationship of skin diseases to bacterial, pollen and food allergy. One is confronted at once with a definition of allergy. If one restricts the term to those instances of an altered state of reactivity in which specific antibodies can be demonstrated by passive transfer or by other tests, many cases of apparently definite allergy will be excluded. On the other hand, if one broadens the concept of allergy to include altered reactivity associated with clinical phenomena in the skin or elsewhere, such as urticaria, anaphylactoid reactions, sneezing, lacrimation, angioneurotic edema and bronchial asthma, one must somewhere try to distinguish between simple intolerance, primary irritation, acquired hypersensitivity and allergy. So little is known and so much is said in a speculative manner that for the present it seems better to speak of allergy in a comprehensive way and to include all suspected as well as definitely proven cases of altered reactivity that follow an incubation period after preliminary exposure to a sensitizing substance. In this category one can then mention some cases of contact dermatitis and light or cold sensitization without drawing severe criticism, because such cases are often instructive and interesting.

Bacterial allergy may result from the disintegration or metabolic activity of microorganisms and is closely associated with immunity. The skin plays an important part in immunity if we are to judge from the tuberculin test, the Dick reaction, the Schick reaction, and the many other skin tests which are indices of the degree of immunity. Bacterial allergy is also commonly manifested in the skin by autosensitization or eczematization, which may be localized to a single area or may be multiple lesions or generalized. Nodular vasculitis, erythema nodosum and a variety of "id" eruptions are probably allergic manifestations in most instances. Often these are caused or related to focal infections. However, Baird[5] postulates that no infection or local immune reaction is necessary and that the bacterial flora on the skin and in the gastrointestinal tract may, by products of bacterial metabolism or by combination of bacterial proteins with tissue proteins, produce allergens which provoke "ids," autosensitization, and other cutaneous allergic manifestations or internal allergic phenomena. This is a broader concept which, theoretically, is possible. Our knowledge is still so elementary that one can only hope that some day there will be scientific confirmation of these hypotheses and elucidation of the biochemical factors of "id" eruptions.

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PUSTULAR BACTERID

The relationship of focal infections to skin diseases and the "id" reaction are intangible subjects in which the presence of allergy may be suspected more or less strongly without clear proof. We have been interested in recalcitrant pustular eruptions of the palms and soles for many years. That

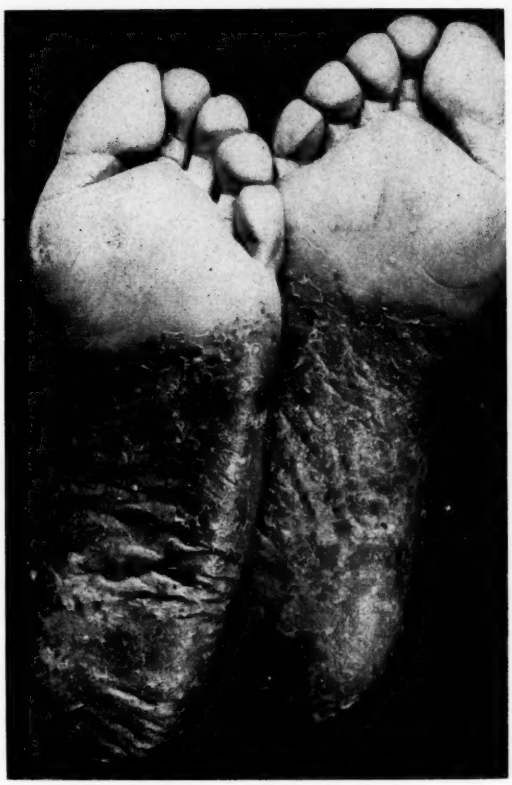

Fig. 1. Pustular bacterid. Characteristic symmetrical patches on soles, consisting of vesicles, pustules, erythema and exfoliation.

some of these cases are caused by focal infections seems well established. In 1935,[1] we reported fifteen cases of pustular bacterid, of which several were cured by removal of foci of infection. A recent review of our records shows that since that time there have been twenty-nine cases which we classified as pustular bacterid. Of these, twelve were promptly and unquestionably cured permanently of recalcitrant pustular eruptions limited to the palms and soles by the removal of focal infections. An additional three patients in this group were cured by antibiotics given orally,

hydrocortisone or antibiotic local remedies. These three cases might have been instances of streptococcus acrodermatitis, but clinically they were pustular bacterid. Seven other patients were advised to have foci of infection removed and possibly did, but these cases were lost for subsequent observation. Of the seven remaining patients, one had chronic

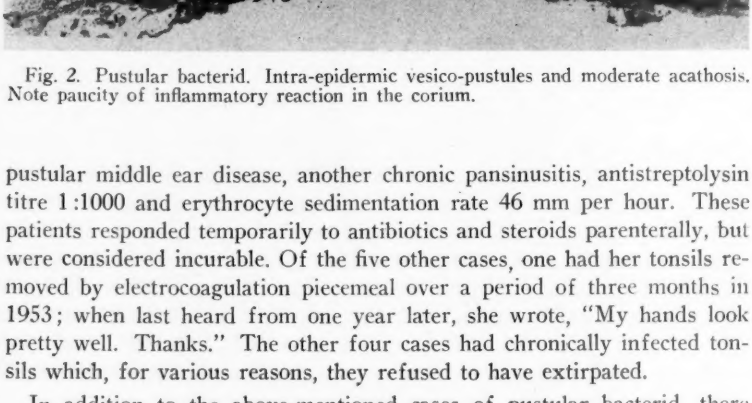

Fig. 2. Pustular bacterid. Intra-epidermic vesico-pustules and moderate acathosis. Note paucity of inflammatory reaction in the corium.

pustular middle ear disease, another chronic pansinusitis, antistreptolysin titre 1:1000 and erythrocyte sedimentation rate 46 mm per hour. These patients responded temporarily to antibiotics and steroids parenterally, but were considered incurable. Of the five other cases, one had her tonsils removed by electrocoagulation piecemeal over a period of three months in 1953; when last heard from one year later, she wrote, "My hands look pretty well. Thanks." The other four cases had chronically infected tonsils which, for various reasons, they refused to have extirpated.

In addition to the above-mentioned cases of pustular bacterid, there were three cases of pustular psoriasis with typical lesions of psoriasis vulgaris and pustular eruptions on the palms and soles. There were also two cases of apparent pustular bacterid accompanied by positive finding of pathogenic fungi on the feet. They were both ultimately cured by a combination of treatments, including the removal of foci of infection and the use of antifungal remedies.

In two other cases, after tonsillectomy there was a temporary cure which after a few months was followed by a recurrence of the same eruption. However, the recurrence in one responded to the local use of hydrocortisone ointment and has not reappeared. This case is not included in the list of twenty-nine definite cases of pustular bacterid. These were the only known failures where the removal of foci of infection was of concern, although there may be others among those with whom we have lost contact. None of these pustular bacterid patients in the last twenty years has shown any clinical signs of psoriasis. Pustular psoriasis of the extermities as described by Ingram[7] and Barber[6] morphologically resembles the pustular bacterid but seems to be a distinct disease. Widespread cases of

pustular bacterid and of pustular psoriasis have been described and the authors have seen a few such cases, but until more is known about these entities it seems foolhardy for us to speculate or to make arbitrary statements about them. It is enough to prove that some patients who have no clinical signs, or family or personal history of psoriasis, develop recalcitrant pustular eruptions on the palms and soles which are cured by the removal of foci of infection, and that after such removal many of these patients remain permanently cured. The pustular bacterids, as originally described, have a tendency to involve the middle portions of the palms and soles symmetrically, the heels and the thenar eminences without affecting the interdigital surfaces, and the outbreaks of pustules or pustulovesicles appear in crops and during such exacerbations there is often a leukocytosis. The histology of pustular bacterid is a large intraepidermal pustule with very little inflammation in the corium. The histology as described in 1934 is distinctive and could not be confused with cheiropompholyx, psoriasis, acrodermatitis continua or dermatophytosis.

INHALANTS

The relation between inhalant allergy and skin disease is a subject of vast importance and equally of great confusion. Certainly the inhalation of bronchial asthma but may also invoke urticaria and dermatitis which is feathers, cat hair and other epidermal emanations may not only produce best described as pruritus with lichenification. In other words, the cutaneous manifestations are usually the result of rubbing to relieve itching. Often such dermatitis is flexural, but it may be worse on exposed parts such as the face, neck and dorsal surfaces of the hands where contact with the offending substances may augment the pruritus. There may be localized erythema and edema from such contact. Parakeet feather sensitivity is common these days and may express itself in this manner. Sensitivity to down in pillows, pollens, and molds may show the same clinical picture.

Sensitivity to molds is another aspect of inhalant allergy, and we may conjecture that mold sensitization may evoke any of the manifestations produced by such mold products as penicillin and streptomycin. We are all familiar with the manifold expressions of penicillin allergy that range from anaphylactic shock to urticaria, local contact dermatitis and generalized exfoliative dermatitis. Sensitization to streptomycin is also common. The fixed type of local erythema with pigmentation that persists and flares up after each dose is not unusual. One nurse in a tuberculosis sanatorium became so sensitized from handling streptomycin that she developed bronchial asthma, giant urticaria and widespread dermatitis from it. After positive patch tests she was transferred from the wards to the business office, but for the past two years she has continued to get outbreaks of urticaria and attacks of sneezing whenever patients who have recently had streptomycin come within close proximity. Such attacks be-

gin within a few moments and apparently are caused by inhalants of expired particles of streptomycin. Another patient, who is a dentist, developed severe redness and puffiness of the eyelids, attacks of sneezing, wheezing and insomnia every spring. He was found sensitive to molds which grew in his cellar where he frequently worked at a hobby. All other tests, both by the scratch and intradermal method to foods and inhalants, were negative.

INFANTILE ECZEMA

The relationship of infantile eczema to food and inhalant allergy is accepted by most practitioners, although many other factors, especially emotional environment and atopic family history, are of equal or greater importance in some cases. Tension between the parents and trauma from alkaline soap and water scrubbing or from urine in wet diapers is enough to provoke a protracted and severe case of infantile eczema. Once started, the vicious cycle of itching, rubbing, eczematization and more itching may take over. The importance in these cases of a detailed, carefully taken history cannot be emphasized too strongly. Skin tests have limited value in most of these cases. Routine elimination diet consisting of prune juice, apple sauce, apricot nectar, rice, oatmeal, corn meal, barley, Rye Krisp, oleomargarine, lamb, beef ground or broiled, baked potato or banana, and soy bean substitute for milk, with a few vegetables such as peas and string beans, is prescribed. Eggs are omitted. Such a limited diet is continued only a couple of months. If it does no good in that time, there is no use continuing it. Pets are not allowed, and antihistaminics are freely used along with hydrocortisone ointment or tar ointment. Sensitization to dog and cat hair is common in children. The emotional environment, spanking, sharp, short commands by a tired ill-adjusted parent are also important factors to be considered.

ECZEMA IN ADULTS

In older children and in adults, skin tests by the scratch, intradermal and patch methods are routinely done. As previously stated, it is not always possible to be sure whether a patient has allergic eczema of internal origin or contact dermatitis and the two may be combined. For this reason, each patient is tested to whatever seems indicated and by various techniques, including passive transfer tests. The value of skin testing by any means other than the patch test has been questioned by many, but our results through the years have warranted continuation of all of the techniques. If it were only for the details added to the history by making the tests, the effort would be worthwhile; but, in addition, there are frequent unquestionable examples of the value of scratch tests to cat, rabbit, and dog hair and to pollens. However, in generalized neurodermatitis with an atopic history, skin testing is of little value, and we fully agree with those who criticize the tests as extremely disappointing. In this connection, one must

realize that all of our methods of testing are extremely crude and that there are manifold ingredients in clothing, cosmetics and environment, especially synthetic or natural resins and emanations, which may play an undiscovered role.

In adults, it is often difficult to distinguish clinically feather or mold allergy with red swollen eyelids from contact dermatitis due to nail polish, hair lacquer and similar contactants. A recent case of hair lacquer dermatitis was interesting because the redness and swelling of the eyelids and dermatitis of the neck and flexures of the elbows began simultaneously with a series of meticortelone injections subcutaneously under a patch of neurodermatitis of the left hand of many years' duration. Patch tests to the hair lacquer were completely negative on the thigh, slightly positive (1 plus) on the arm, and one "squirt" of the lacquer on the neck produced a severe dermatitis. This illustrates both the intricacies of patch testing and the localized type of sensitization to an area previously exposed to the sensitizing agent, which is even more powerfully illustrated by the Shwartzman phenomenon. Another patient with persistent dermatitis for two years, mostly on the face, ears and hands with a few spots on the shoulders and forearms, presented a case sufficiently dramatic to be reported. Because of the localization chiefly upon exposed parts, contact dermatitis was suspected, but the history was that the trouble began while en route through the Panama Canal to San Francisco, persisted for six months in California, and then for another eighteen months in New York. Hospitalization and cold boric compresses caused the eruption to disappear in one week. Then tests were started by scratch and intradermal techniques to foods, inhalants and, lastly, by patch tests to about 100 common contactants. The only positive test was a strong reaction to a well-known insecticide. The history showed that while passing through the Panama Canal this insecticide had been sprayed to keep away mosquitoes, and in California the same brand of insecticide had been used for the same purpose. At his home in Yonkers, New York, no insecticides were used except a moth-preventative that was sprayed in the apartment. Patch tests to it were strongly positive. An attempt was made to clean his home of all of the moth-preventative. All floors were washed and waxed, all closets cleaned, all rugs aired in the sunshine and beaten, all clothes cleaned. He went home happy and completely well and the next morning telephoned that he was all broken out again in the usual sites and was terribly depressed. He was hospitalized again and his home was carefully inspected. It was discovered that the coat closet near the entrance had not been cleaned although the spray had been used there also. It was, with all of its contents, then cleaned thoroughly. The patient, again having recovered in the hospital, went home and never had any further skin trouble. This case is described to illustrate what a minute exposure will suffice to produce an exacerbation. It gives foundation to the suggestion that one reason why we frequently fail to cure patients who have positive

intradermal tests to foods is that the diet we allow them is contaminated by the emanations of common allergens such as eggs and wheat which are kept in the same refrigerator or kitchen cabinet with foods that are permissible.

It is regrettable that the olfactory functions of humans have deteriorated through the ages. My home in the country is miles from other habitations and there are no dogs there except our beagle bitch. But when she goes into heat, and long before, we can detect the fact; there will be a circle of male dogs on our grounds, staying there without food or water, waiting for the poor little beagle to go outside.

Animal and vegetable emanations arise not only from animals and plants, but also from the chops, chicken, vegetables, dairy products and breadstuffs in the ice box or kitchen cabinet. Fabrics made of wool, cotton or silk are often mixed with rayon and a chemical filler, a dyestuff, and a finish that imparts luster. Some fabrics are also mothproofed, waterproofed and are made noninflammable. Emanations, resins and dusts are a vast world in themselves. We know little about them and their physiologic impacts. Specific alterations of reactivity in the cells of the skin or other parts of the body, in the intercellular fluid or collagen, or in the circulating blood are subjects of vast importance which piece by piece are being slowly elucidated.

Allergy is also a theoretical explanation of the self-healing (Ferguson-Smith[8]) type of epithelioma and of the spontaneous regression of other types of cancer. It is presumed that the nucleoproteins of the cancer cells are allergens and lead to the self-destruction of the cancer cells, similar to the Rh factor phenomenon in erythroblastosis neonatorum.

SUMMARY

The roles of bacterial, pollen and food allergy as a manifestation of some skin diseases are discussed. Pustular bacterids of the hands and feet diagnosed in twenty-nine cases, some of which have been under observation for twenty years, are reported. The removal of focus of infection brought unquestionable and permanent cure in twelve of these cases. The other seventeen cases are discussed in respect to foci of infection.

Skin manifestations of inhalant allergens such as feathers, pollens and molds are described. The relationship of food and inhalant allergens to infantile eczema, as well as to eczema in adults, is reported from the standpoint of the value of various patch, scratch and intradermal testing. Allergenic emanations from animals and plants are still within the realm of speculation regarding the exact mechanism of effect.

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ERRORS IN THE APPLICATION OF THE SCIENTIFIC METHOD

In the application of the scientific method to the problems of medicine, the possible errors are infinite, whether they be in observation, in correlation, in formulation, or in experimental proof of hypotheses. A recent study by Ross (Ross, O. B., Jr.: Use of Controls in Medical Research, J.A.M.A., 145:72, 1951) on the use of controls in medical research was based on a review of one hundred consecutive and unselected current medical journal articles describing some procedure or therapy for disease. In 45 per cent of these papers, the investigators made no attempt to compare results of the specific therapy described to those in an untreated group. Eighteen per cent more used controls considered inadequate. In commenting on his findings, Ross emphasized the necessity of maintaining a skeptical attitude toward all reports, however enthusiastic, unless the personal bias of the investigator and the variability of the disease itself were corrected for, by setting up rigid controls. Of course, there is also an implied criticism of editorial acumen because all of the papers studied appeared in first-rate journals.—Editorial by FREDERIC D. ZEMAN, M.D., *J. Chron. Dis.* (Dec.) 1956.

ENZYME ACTIVATION IN ALLERGIC REACTIONS

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FRIEDBERGER,[13] in his original papers which launched the humoral theory of anaphylaxis, suggested that antigen-antibody precipitates, when added to normal guinea pig serum, adsorbed upon themselves a complement-like ferment from the serum which brought about a degree of proteolysis, resulting in the appearance of an *anaphylatoxin*. A few years later Bronfenbrenner[5,6] and Jobling,[17,18] independently, confirmed the capacity of antigen-antibody precipitates, and also of nonspecific adsorbing substances, such as agar or kaolin, to activate a proteolytic autodigestive process in serum, accompanied by the development of an anaphylaxtoxin. These authors postulated that activation of a blood protease, and a simultaneous reduction in antitrypsin, were primary events in anaphylactic reactions, and Bronfenbrenner,[6,7] especially, emphasized the suggestion that the desensitized state might be explained by the presence in body fluids of an excess of antiproteolytic substances. With the coming into favor of the cellular-histamine theory of Dale,[11] however, the idea that anaphylatoxins, whether formed by proteolysis or otherwise, were significant in anaphylaxis was generally abandoned.[12]

It was not until about twenty years later that new experimental evidence, again implicating proteolytic phenomena, and once more indicating a significant role for humoral as well as for cell-fixed factors in allergic reactions, was forthcoming, principally through the work of Rocha e Silva and collaborators.[36-40] More recently, Ungar,[44-47] Humphrey and Jacques,[15] McIntire et al,[26-28] Becker,[3,4] and others, have studied the postulated role of proteases, and have contributed to the reviving interest in the protease activation theory.[8]

Proteases and anaphylatoxins, once regarded as of significance only in relation to the classic humoral theory of hypersensitivity, are now being assigned basic roles in the cellular concept as well, as mediating agents in the release of histamine, serotonin, heparin, and other physiologically active substances from body cells. An important result of these developments is the current recognition that *both* cellular and humoral factors contribute to the chain of events which follows union of antigen with antibody in the hypersensitive individual.[9] The cellular and humoral

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theories, once thought of as irreconcilably opposed to one another, are now complementing each other in a broader concept.[9,37,44]

Most investigators have quite naturally assumed that if any protease is involved in allergy it is most likely to be *plasmin,* the fibrinolytic enzyme of blood. Plasmin is formed by activation of its precursor *plasminogen.*[1] Conversion of plasminogen to the active enzyme can be brought about (1) under the direct influence of various kinases or *activators* present in certain tissues, in spontaneously fibrinolytic blood, and also in such body secretions as tears, milk, or urine; or (2) indirectly, through the preliminary conversion of a *proactivator* to an activator. The streptococcus product *streptokinase,* widely used as a plasminogen converting agent, first reacts with the proactivator in body fluids to form activator, which in turn changes plasminogen enzymatically into active plasmin.[31,42] Natural inhibitors exist for these reactions,[32] and the inhibitors of plasmin are not identical with trypsin inhibitors.[43]

Although there are some aspects of this complex plasminogen-plasmin system still not fully understood, it is clear that it constitutes a basic physiologic mechanism,[1] with important functions, and it would be reasonable to expect some involvement of this enzyme system—some change in the balance between the fibrinolysin and its inhibitors and activators—in so profound an upset as a severe allergic or anaphylactoid reaction. Evidence has been obtained showing that an increase in the total potential proteolytic activity of the blood does indeed occur in anaphylactic and peptone shock, at least in dogs[18,19,39] and in human beings.[10,24,29] In a remarkable experiment, Lowell and collaborators[24] inoculated a group of hay fever patients intravenously with the allergens to which they were sensitive, and during the ensuing reactions clotted blood samples from three of the six individuals became lysed spontaneously within less than twenty-four hours after collection, indicating that an abnormal activation of the blood fibrinolysin had occurred. With the method developed in our laboratory[29] for testing the proteolytic activity of whole human serum, we found that sera collected during an acute asthmatic attack exhibit a total potential proteolytic capacity more than double that of serum from normal persons. Activated fibrinolysin may contribute in as yet undefined ways to the pathology of certain hypersensitivity reactions. At least one of the smooth muscle contracting substances which may appear in the plasma during anaphylactic or peptone shock, bradykinin, is formed as a result of activation of the blood fibrinolysin.[38]

Nevertheless, it does not necessarily follow that plasminogen activation has a *primary* role in initiating the hyperergic response, or that plasmin itself is directly responsible for the characteristic symptoms. A formidable obstacle to the ready acceptance of such a view lies in the well-established fact that the fibrinolytic blood protease may be liberated in many entirely unrelated pathologic conditions having none of the characteristics of allergy.[1,8,10,25,30,33,35,41] Moreover, purified preparations of

plasmin and of streptokinase may be given to normal human beings by intravenous infusion without stimulating allergic responses, or other important pharmacologic or biochemical changes.[2]

Furthermore, studies conducted by several groups of investigators to determine the mechanism of histamine (and serotonin) release from white blood cells[26-28] or platelets[15] or from the perfused tissues of hypersensitive animals[37] have shown that streptokinase-activated fibrinolysin preparations by themselves have at best only an irregular (and rather poor) histamine-releasing action, in comparison with that of serum or plasma in which a specific antigen-antibody reaction has occurred in the presence of complement. The anaphylatoxins prepared by Rocha e Silva[37,40] from rat and guinea pig plasma, which release large amounts of histamine by perfusion through the lungs of normal guinea pigs, and which also produce a marked contraction of normal guinea pig ileum, were not themselves proteolytic. Although Ungar[46,47] has presented evidence indicating a correlation between the amount of protein breakdown in animal tissues and the quantity of histamine released, his data do not establish a definite causal relationship between fibrinolysin activity and histamine release. It appears that we shall have to dismiss plasminogen activation as an *essential* mechanism for bringing about the allergic response. On the other hand, the possible damaging action of high concentrations of active plasmin which might be reached in localized tissue reactions, the disrupting effects of abnormal fibrinolytic activity in the circulating blood on hemostatic mechanisms, and perhaps other injurious influences, may yet be found important in the pathogenesis of some allergic manifestations. Obviously, more investigative work is needed.

In the meantime, a protease-activation theory of allergy need not be abandoned altogether, unless such a theory is made to stand or fall solely on proof of an essential role for the fibrinolytic enzyme system. There remains a considerable body of evidence, accumulated through the years, indicating that a different enzymatic process of some kind *is* activated by antigen-antibody aggregates, and participates in the rapid formation, from complement-containing normal plasma, of an agent (anaphylatoxin) capable of causing release of histamine, serotonin, heparin, and other metabolites, from body cells. There is a striking analogy between the conditions necessary for the formation of a potent tissue-histamine-releasing "anaphylatoxin" from fresh serum or plasma by antigen-antibody reactions[5,38,40] and those required for the release of histamin *in vitro* from blood cells or platelets by contact with antigen-antibody preparations.[15,28] In all these phenomena, a heat-labile blood component supplies a necessary ingredient in the plasma which is changed in a few minutes to an active histamine-releasing agent. This transformation has the character of an enzyme reaction; the process is highly dependent on temperature, and on the ionic strength of the solutions. It is inhibited irreversibly by citrate and to a lesser degree by oxalate and salicylate. All investigators,

from Bronfenbrenner on, have agreed that the essential participant from blood is probably *complement,* or a part of the complement complex.

The experiments of Ungar[45,47] and of Geiger[14] which have demonstrated the appearance in fresh serum or plasma of a transient proteolytic activity

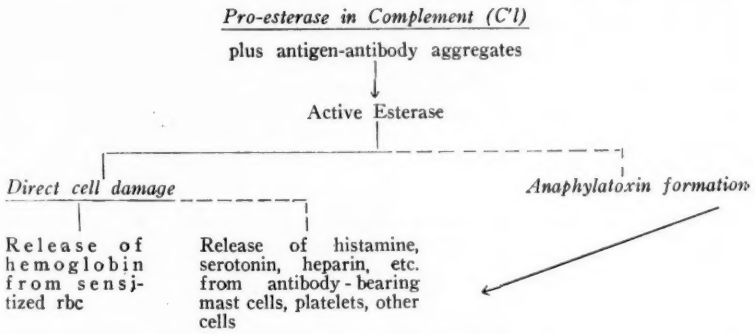

Fig. 1. Possible role of complement esterase in allergy.

after mixture with antigen-antibody complexes, or with various polysaccharides and other "anaphylactoid agents," have again emphasized the essential role of a complement-like factor. The absence of this factor appears to explain the negative results of others in similar experiments.[16] We have previously called attention[8,9] to the provocative work of Kulka,[20] who showed that regular contractions of a strip of *normal* guinea pig uterine tissue in the Schultz-Dale apparatus could be obtained when antigen and antibody were made to combine in the fluid surrounding the tissue, provided a small amount of fresh (i.e., complement-containing) guinea pig serum was also added to the bath.

A most significant recent development is the recognition that complement need not be considered merely as a kinase or necessary adjunct for some sort of enzymatic process in these phenomena, but instead it may itself be a source of an active enzyme. Lepow and collaborators[21-23] and Becker,[3,4] working independently, have brought convincing evidence that the first component of complement, C'1, is an esterase which exists as an inactive precursor in the blood, and is changed to active form during reaction with sensitized red blood cells, or when put in contact with other antigen-antibody aggregates. An active esterase can be eluted from such aggregates after treatment with fresh human serum.[22] We thus have unequivocal evidence that an antigen-antibody reaction is capable of changing a naturally-occurring blood enzyme from an inactive to an active state. And in the active form this enzyme can injure cells, (namely red blood cells), releasing hemoglobin.

In Figure 1, the possible role of the complement esterase in allergy, essentially as suggested by Becker,[4] is indicated. In this diagram we are

now sure of only the activities indicated by the solid lines. The rest is speculative. But here we have a renewed basis for an enzyme theory of allergy and in a more precise form than before.[4]

To me the most notable result of the current research into allergic mechanisms reviewed here is the rescue of hypersensitivity from its former peculiar isolation as a biologic phenomenon dependent upon an exclusively cellular antigen-antibody interaction, as though the body fluids simply did not exist. There is no longer any reason to doubt that both blood-borne and cell-fixed factors play significant parts. Allergic reactions are finally being brought into line with other physiologic, adaptive responses to stress and shock.

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Progress in Allergy

PEDIATRIC ALLERGY
A Critical Review

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THIS REVIEW encompasses the literature on pediatric allergy of interest to the pediatrician and pediatric allergist published since the last review of the series in 1955.[51] It, therefore, covers the literature of the past three years.

ATOPIC DERMATITIS

Hill, in a series of five articles[121] which were subsequently published in book form, has written a very detailed discussion of eczema in infants and children. This is an excellent discussion of the whole subject with a complete discussion of the subject of atopic dermatitis, differential diagnosis and detailed treatment, all of which is based on Dr. Hill's own long experience in this condition. It is extremely well written and is recommended reading for all physicians who look after eczematous infants and children.

Overall[187] presents a general discussion of the treatment of atopic eczema. Buffum,[39] in a similar discussion, stresses the very great need for preventing the development of severe asthma following infantile eczema.

Lobitz and Dobson[148] claim that people with, or susceptible to, atopic eczema have abnormal physiological findings, such as, pallor, dry skin, an abnormal type of whealing, low blood pressure, hyperreactivity to the cold pressor test and an abnormal reaction to the injection of histamine or acetylcholine, as well as sweat retention phenomena and sometimes cataracts. They feel these are of help in establishing a diagnosis and that both allergic and psychosomatic factors must be considered.

Jillson and Piper[131] stress the role that inhalant allergens play in the etiology of atopic dermatitis. They feel that it is the forty-eight hour delayed skin reaction which is of value in determining the causative allergens and find desensitization beneficial, but they stress that low dosages must be used or there will be a flare-up in the rash.

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Dr. Ratner is now deceased.

Tuft[252] also stresses the role of inhalant allergens in the etiology in atopic dermatitis. His paper is based on a study of seventy-six patients who were first seen at from one to twelve years of age. Investigation revealed that large numbers of these patients gave positive skin tests with house dust and many with pollens, molds, animal danders, etc., and he satisfied himself that in many cases these positive tests were of etiological significance. Often the importance was indicated by history. Sometimes the rash was flared up by deliberately exposing the patient to the allergen in question or by giving an injection of the allergen with a subsequent flare-up in the dermatitis. Tuft finds that in infants foods are considerably more important than inhalants, but in children with eczema the inhalants are more important than foods. He also recommends desensitization but again stresses the need for using low doses. With this form of treatment he obtains good results.

Ratner,[198] in a general review of infantile eczema, also emphasizes the importance of inhalant factors.

Diamond,[66] in a series of 526 cases of allergy, had sixty-three with allergic dermatitis, and in these cases the etiology was inhalants and the patients did well with hyposensitization therapy, provided the doses were kept small, smaller than are usually used in the treatment of respiratory allergy.

Farmer[77] investigated his patients with eczema by means of scratch tests and found reactions to the inhalants in both children and adults. He feels that these reactions are clinically significant as to the etiology of atopic eczema.

Every year there are new papers out stressing the importance of inhalants in the etiology of atopic dermatitis and stressing the value of hyposensitization, and yet a great many physicians are still sceptical about this. Anyone who will thoroughly investigate these patients, determine the responsible inhalant agents, and hyposensitize with a low dosage method will be greatly impressed by the beneficial results which are obtained. Most of the scepticism is due to seeing patients who have not been thoroughly investigated or who have been hyposensitized with too high a dosage schedule, and in either case the results are bound to be poor.

Strauss and Kligman[237] take the opposite point of view. They claim that hyposensitization and avoidance of exposure to allergens is usually unrewarding in the treatment of atopic dermatitis. Admitting that there is certain evidence in favor of an allergic etiology, they point out that flare-ups which are provoked by hyposensitizing injections, inhalation or ingestion of allergens always occur at the site of the pre-existing lesions or at healed sites, not in absolutely normal skin. They had eight adult experimental subjects who gave strong reactions with either short ragweed or crab and seven who had an atopic background of asthma and/or hay fever. Daily topical application of specific atopen at the same site

for three weeks failed to produce a dermatitis, although most of the subjects exhibited wheals and some reacted with asthmatic attacks or hay fever, indicating the atopens had been absorbed. However, the application of Rhus toxicodendron antigen to the same subjects who were sensitive to poison ivy produced definite allergic contact dermatitis, and when these subjects were given the antigen of short ragweed and crab by daily topical application, by intranasal instillation or by subcutaneous injection, six of the eight produced a definite exacerbation of dermatitis accompanied by marked itching. The authors believe this demonstrates that introduction of these allergens by any one of the three routes causes a flare-up of the existing area of contact dermatitis due to fixation of the protein antigens in the site of inflammation. They feel, therefore, that atopy is frequently associated with a characteristic type of dermatitis but is not its basic cause. In other words the allergic mechanism acts in a secondary fashion on any primary dermatitis of unknown origin.

Although this piece of work is very interesting in that it demonstrates one method by which an allergen either applied to the skin or entering the body by some other route can cause dermatitis, it does not in any way prove that typical atopic dermatitis is not caused usually by the inhalation of inhalant allergens. For reasons we do not know, in atopic dermatitis there is a predisposition for certain areas of the skin, such as the antecubital or popliteal fossae, to be involved, particularly in childhood. If the natural course of this disease is for the rash to be confined to these areas it is not at all unreasonable that hyposensitizing injections containing the responsible allergens should cause the rash to appear in the same areas as opposed to the absolutely normal skin. If an area of normal skin is made abnormal by some artificial method, such as the application of the Rhus toxicodendron antigen, and the inhalant allergen then produces an area of atopic dermatitis at that site, it does not in any way invalidate the hypothesis that normally inhalant allergens produce it in the so-called sites of predilection. In addition, as it has already been stressed, hyposensitization with inhalant allergens in atopic dermatitis if properly carried out is usually very rewarding and this is very good evidence that inhalant allergens are one of the important causes of the disease, although it must be admitted there are certain unknown factors, such as, the sites of predilection and the reasons why some people respond to the inhalant allergens with atopic dermatitis and others with asthma.

Vowles et al[260] followed eighty-four patients with eczema in whom the condition had begun before one year of age and in whom hospital admission was necessary because of the severity of the disease. At the time of the follow-up the patients ranged in age from ten to over twenty, and six had died during infancy. As controls they used fifty-seven surgical patients of the same sex and about the same age with no history

of skin disease and another 120 school children of the same age and sex with no history of eczema. In 55 per cent of the seventy-eight patients followed the eczema persisted up to the age of thirteen years, and there was a great tendency for its clearing during the first three years, which occurred in 27 per cent of cases. Seventy-three per cent of the eczema patients subsequently developed respiratory allergy, as compared with 5 to 7 per cent of the control group, and 22 per cent of the eczema patients developed pneumonia, with only 2 per cent in the control group. They feel that in the eczema patients skin disorders are likely to last longer when there is a family history of eczema or when the skin is greasier or drier than normal, but they could not find any other factors, such as, sex, type of infant feeding, etc., which appeared to influence the tendency to persist.

There is no mention at the end of the paper whether hyposensitization was carried out on these patients and, therefore, probably it was not. One cannot help wondering whether the figures would not have been greatly different as to clearing of the rash and a lower incidence of the development of respiratory allergy if these patients had been investigated and hyposensitized with our present methods.

Finn[82] also attempted a long term prognosis in infantile eczema. He did a twenty-year follow-up on 136 cases of infantile eczema by questionnaire, but obtained useful replies in only thirty-seven. Of this group, 27 per cent had suffered respiratory allergy but no childhood eczema, 19 per cent had suffered childhood eczema but no respiratory allergy, 21 per cent had suffered both respiratory allergy and childhood eczema. Of the total of the thirty-seven patients, twenty-five described at least one of the recognized sequellae of infantile eczema.

Huntly and Dees[127] report five cases with a combination of chronic eczema, thrombocytopenic purpura and chronic suppurative otitis media with fatal outcome. They believe this is a definite clinical entity. All of these patients appeared to be allergic. All suffered from repeated infections. Four had eosinophilia, ranging from 14 per cent to 45 per cent. Cause of death was always infection, four dying at approximately two years of age and one living until seven-and-a-half years of age. In four cases a splenectomy was done with only a very temporary platelet rise. Three of the five children had family histories compatible with transmission of this disease as a sex-linked recessive trait. Determinations of gamma gobulin and serum protein patterns were done in only the last case and were normal.

Herlitz[118] studied eighty-three cases of infantile eczema. Patients in all cases received the same treatment except that alternate ones had cultures taken from the eczematous lesions and also from the pharynx, and the organisms were tested for sensitivity and all found to be sensitive to either penicillin and/or sulfa. These patients were treated with these drugs. For final analysis there were twenty-four treated patients and

thirty-one untreated, with seemingly no difference between the two groups. Herlitz also failed to find conclusive proof of sensitization to the isolated bacteria by skin tests.

Meara[172] studied 112 children with infantile or childhood eczema and forty-three children with other skin diseases as a control group by means of scratch test. While the control group had negative reactions, 65 per cent of the eczema patients gave positive reactions to one or more test substances. In the younger children egg or other foods were chiefly important. In the older children pollens were more frequent. Tests were repeated in sixty-eight children six months later and the reactions were virtually the same in 85 per cent. There appeared to be no relationship between the incidence of positive reactions and the severity of the skin disease. The author could find very little correlation between removal of egg from the diet and the course of the rash. Six children who reacted only to pollens were given a course of injections which did not appear to affect their eczema. The author, therefore, feels that while skin tests may be of some diagnostic significance they are not too much help.

The authors of this review feel very definitely that skin tests are extremely useful in the investigation of infantile or childhood eczema with the reservation, of course, that they are merely a tool for investigation and have to be interpreted intelligently if they are to be used to help patients. Actually, there is not enough data given in the above paper to demonstrate this is not true. In spite of a positive reaction with egg, one cannot expect much effect on the rash by withdrawal of egg from the diet unless all other factors are taken into consideration at the same time, and the same thing applies to the course of hyposensitizing injections with pollens. Most of these patients have multiple etiological factors, very rarely only one, and this is the reason skin tests are necessary for full appraisal, but, of course, all the etiological factors that can be determined must be taken into consideration in the treatment if a successful outcome is to be achieved.

Nisenson,[183] in a study of twenty-four hospitalized cases of atopic eczema, found that twenty had evidence of hypoproteinemia and eight had clinical evidence of edema, the latter caused by extensive weeping of the skin, diet poor in animal protein and infection. He, therefore, recommends that in extensive eczema, particularly where soybean milk is used exclusively, meat should be introduced at an early age, and the patient may also be treated with amino acid feedings, amigen, plasma or blood. He found that poor diet alone, without excessive weeping or infection, rarely produced marked hypoproteinemia.

Baer et al,[11] in a symposium, discuss in considerable detail the dermatologist's viewpoint of atopic dermatitis, including history of the disease, clinical picture, differential diagnosis, etiology, physiology and theories of pathogenesis.

Loewenthal et al[149] in another symposium by ten authors, give a rather complete review of the subject of atopic eczema including the skin conditions which may be confused with it.

Baer[9] edited a book on atopic dermatitis which has articles by five different authors, again presenting the dermatologist's view of atopic dermatitis. The role of allergy is considerably minimized, and there is a great deal in the book which the allergist would disagree, but it is good presentation of one side of a very difficult subject. Much of the material in this book is similar to the previously-mentioned symposium by Baer et al.

STEROIDS IN ATOPIC DERMATITIS

O'Keefe[185,186] reports nine cases of infantile eczema in which he carefully determined the etiological factors by history, with emphasis on foods. He then initiated cortisone therapy to almost completely clear the skin and then, by changing foods in the diet, determined which foods were important and which were not important. After the skin was completely cleared he gradually decreased the dose of cortisone until it was eliminated altogether and kept the skin clear, although he subsequently added foods which originally caused the rash. He feels this is the most satisfactory way of using cortisone in eczema, because it is dangerous to use the drug over long periods of time and it is only by controlling the responsible factors that one can get off the drug without the rash becoming worse.

Ingram et al[128] report the use of ACTH and cortisone in fifty-two cases of eczema. Most of these were adults with long-standing disease. In the vast majority the drugs were effective in helping the patient. In general the more acute manifestations tended to disappear, while the lichenified lesions persisted and relapses invariably occurred when the drugs were withdrawn. Complications to the therapy were not severe.

Robinson[208] reports the use of prednisone in four patients with atopic dermatitis. Improvement appeared within five to seven days and the lesions were completely cleared in fourteen to twenty-one days. The maintenance dose was 7½ mgm daily in the one child, 15 to 20 mgm daily in the three adults. No serious side effects were noted. When the dose was reduced below the maintenance dose, symptoms recurred in all.

Kalz et al[134] reports on the use of hydrocortisone ointment in a total of 581 patients with various skin diseases. Among these were seventy-five cases of atopic dermatitis, 8 per cent of which showed equivocal improvement. In 66 per cent the ointment was found to be a useful therapeutic adjunct. In 21 per cent the rash was controlled while the ointment was being applied, and in 5 per cent there was a full remission lasting for at least two months. The infantile eczema group consisted of 131 patients with atopic dermatitis, seborrheic dermatitis and primary irritant and contact dermatitis in infants and children together with a large number

of cases where diagnoses could not be established for certainty. Of this group, one showed equivocal improvement. In 15 per cent the ointment was a therapeutic adjunct, 24 per cent were controlled while the ointment was being applied and 60 per cent showed a full remission lasting for two months. In the whole series of 581 cases there were twelve instances of irritation or exacerbation of the skin condition, but the ointment base was found to be responsible in all cases.

Church[47] reports on the use of hydrocortisone ointment in 105 cases of which thirty, both adults and children, had atopic eczema. Nine patients healed completely, thirteen improved, six showed no response, and two became worse. Most of the cases which responded to treatment showed maximum improvement within a week. The more lichenified and chronic the eczema, the less effective was treatment, and in these resistant cases the 2½ per cent ointment did not seem to be more effective than the 1 per cent.

Russell et al[214] report on the use of hydrocortisone ointment in 132 patients, of whom twelve had infantile eczema and twenty-two childhood eczema. This was a controlled study with the ointment being used for one week and the ointment base for another week, neither the patient nor the attending physician knowing which preparation was being used. Even though 2½ per cent ointment was being used the authors felt the results were quite poor. However, because of the expense of the ointment they were using it only on small areas which were more severe than the general rash.

Robinson[210] used fludrocortisone ointments and lotions in ninety-six patients with various dermatoses, including atopic dermatitis. Good therapeutic results were obtained with concentrations as low as 0.1 per cent.

Robinson et al[209] report a series of 1,067 patients treated with nine alpha fluorohydrocortisone for various skin conditions, including atopic dermatitis. The 0.1 per cent preparation was found to have about the same benefit as 1 per cent hydrocortisone ointment. Absorption studies showed that there could be some absorption of this product with interference of electrolyte balance.

Marsden and Morgan[163] report on a five-month-old infant who was admitted to the hospital because of eczema. Sixty-eight hours after admission it was noted the skin had cleared, the child was very pale and quiet with a temperature of 107°, and seemed about to die. He was treated with cortisone and responded dramatically. The ninth day after admission the same symptoms appeared and again cortisone led to prompt response. The authors believe this is an acute adrenal failure due to the added stress of hospitalization and state that this sudden collapse and death occurring within a few days of admission for eczema has been frequently reported. This is obviously a condition which demands prompt treatment and apparently cortisone is the treatment of choice.

URTICARIA AND ANGIONEUROTIC EDEMA

Several papers have appeared on the problem of urticaria. Steinhardt[235] reviews 500 cases of urticaria seen in the hospital over a twelve-year period. These patients were of all ages, the majority being in the third and fourth decades of life. Thirty-one per cent had a positive family history of allergy and 43 per cent had a positive personal atopic history. Of the 500 cases, 256 were considered worth being skin tested and, of these patients, 59 per cent demonstrated positive reactions which were regarded as significant. Therefore, skin tests were helpful in establishing the etiology in only about 30 per cent of the total. Etiological factors were foods in approximately 30 per cent of the cases, drugs in approximately 25 per cent, psychogenic factors in approximately 15 per cent, infection in approximately 14 per cent, physical and contact allergies in approximately 6 per cent and undetermined causes in approximately 20 per cent. Thirteen per cent had complete recovery through removal of the causative factor. Seven per cent did not respond favorably to any method of treatment.

Schwartz[221] on the basis of a study of twenty-seven cases of urticaria in children, most of them lasting for only a few days without recurrences, felt that urticaria in childhood usually does not seem to be of allergic origin but thinks it is possibly a manifestation of a specific exanthem of unknown but infectious etiology.

This group of cases is, of course, a very selected one. Urticaria in children, although often of short duration, frequently lasts longer and can become quite chronic and a considerable problem. Many cases, particularly those of long duration, on proper investigation, will be found to be due to foods, drugs, bacterial allergy and sometimes, particularly in the older children, on a psychosomatic basis. Skin tests sometimes are useful but frequently are not of use in determining the etiology.

Winkelmann[270] gives a detailed discussion on the subject of chronic urticaria. He classifies it as due to chemical agents, physical agents, allergy, neurogenic causes and causes associated with systemic disease. Treatment consists of general measures, such as, removal of allergens, dietary restrictions and drug therapy, particularly with the use of antihistamines. He feels that a good deal of chronic urticaria can be avoided if the original acute urticaria is suppressed long enough and suggests that antihistaminic therapy be continued for a minimum of two weeks. He feels that only some cases of chronic urticaria are due to allergy, most being due to other factors.

Mitchell et al[176] studied 187 cases of chronic urticaria, and on follow-up by questionnaire conclude that chronic urticaria is not an allergic manifestation but is usually caused by emotional factors. Positive skin tests by the prick method were found in only 6 per cent and in no instance could they obtain unequivocal evidence to identify specific ex-

trinsic allergy to foods or inhalants as a cause of the urticaria, and they did not find that focal infection was a significant factor either.

Sheldon et al[224] have written a very complete review of the subject of urticaria, giving considerable detail on the four main causes of urticaria—drug allergy, food allergy, infections and psychic factors. This is an extremely comprehensive review.

MISCELLANEOUS SKIN DISEASES

Salles-Gomes et al[216] report on one case of a child with eczema who was exposed to a vaccination and developed eczema vaccinatum only at the sites of the eczema. The virus was definitely identified after isolation. They claim this is the first reported case where there was strict localization of the lesions to the eczematous areas.

Galloway and McBean[90] report a case of generalized vaccinia in a five-month-old child. There had been no previous skin lesion and the distribution of the lesions was in keeping with hematogenous spread. The virus was recovered and identified. The authors state that the mortality rate in generalized vaccinia in childhood is about 90 per cent and is more likely to occur in people with eczema or burns.

This case is interesting in that it is extremely rare for this condition to occur in the absence of preexisting eczema. However, many people would not agree that the mortality is as high as these authors state.

Lundstrom,[156] in a discussion of the complications of smallpox vaccination, discusses eczema vaccinatum. He points out that vaccinia immune gamma globulin is very effective in its treatment and that the administration of this substance concurrently with vaccination would be useful in persons with eczema who must be vaccinated for exposure to infection. If vaccinia immune gamma globulin is not available ordinary gamma globulin is worthwhile but is a great deal less effective. Fox and Pica[85] also report the use of vaccinia immune globulin in the treatment of vaccinia.

Feldman and Newman[80] report on eight cases of Kaposi's varicelliform eruption and in three of their cases there were recurrences, although these are uncommon.. They treated their patients with aureomycin but did not feel that they could properly evaluate this treatment because of the variable course of the disease.

Weidman and Sawicky[265] review the case records of 516 patients with nummular eczema and report a follow-up study on 125 of these, ranging from infants to old adults, but the condition was most common in the young and middle age groups. Eleven per cent gave a personal history of allergy and 15 per cent a family history of allergy. Vioform, tar preparations and hydrocortisone ointments all seemed to help. The authors do not believe this is a typical atopic disease.

Harris and Schick[113] describe the appearance of the rash of erythema neonatorum as an erythema appearing in the newborn infant and pro-

gressing to macules, papules and pustules, the latter containing a great many eosinophiles. This rash is extremely common in newborns, and they feel it is due to specific sensitization of the baby to maternal protein substances which pass via the placenta *in utero*. The sensitization however has no influence on the development of major allergies.

Baer[10] edited a booklet on allergic dermatoses which is a very excellent review of physical allergy as related to the skin, particularly hypersensitivity to trauma, eczematous and polymorphous hypersensitivity to light, urticarial hypersensitivity to light, hypersensitivity to heat and cutaneous sensitivity to cold.

Fromer[87,88,89] has written three reviews on dermatologic allergy which thoroughly cover the field of this subject since the last pediatric review was written.

ASTHMA

Buffum[38,40] has written two papers on the diagnosis of asthma in infancy. He points out that it is sometimes difficult to make a definite diagnosis of asthma at this age. The diagnosis is based on three things: one, the patient should have recurrent wheezing, two, the patient should be demonstratively allergic, and three, the patient should not have any other condition which could cause wheezing. Sometimes it is impossible to make a definite diagnosis and one may have to wait weeks or months before a definite diagnosis can be made. However, he does not feel the term asthmatic bronchitis is useful. If the baby or child has repeated attacks of wheezing with colds he is probably asthmatic and a definite diagnosis should be made if possible. If this is not possible he should be temporarily treated as an asthmatic. He had twenty-six infants who wheezed with colds, followed for more than two years and most of them for five or ten years. All were treated as asthma. Half of them wheezed sometime during the last year of follow-up. Of six that had had severe eczema and positive skin tests, all were still wheezing. Of eighteen with mild eczema and some positive skin tests, fourteen were still wheezing. Of eighteen with no eczema and negative skin tests, eleven were perfectly well. However, he feels that they were all suffering from asthma, although in different degrees of severity.

Dees[61] reviews the incidence of asthma reported from various parts of the world. Her own figures are 9.3 per cent of all pediatric admissions to Duke University Hospital in one year. She also reviews the literature on the incidence of asthma following allergic rhinitis and reports long-term follow-ups on her own asthmatic patients, a total of 236 patients under fourteen years of age. On follow-up after two years, 44 per cent were either cured or greatly relieved, 36 per cent were still having mild asthma and 20 per cent, severe asthma. There was only one death. In 1953 there were 6,737 deaths from asthma in the United States, which is almost as high an incidence as from leukemia or con-

genital heart disease. There were 160 deaths under five years of age and eighty under one year of age. Asthma kills five times as many people as polio, but unfortunately more accurate statistics need to be collected on the incidence and prognosis of asthma in order to fully publicize this fact. Such figures, of course, are essential if we are ever to obtain the recognition for allergic children that is given for other diseases from which children suffer.

Wright[274] in a discussion of asthma in children, stresses that attacks of asthma are really a multiple factor disorder, and these are constitutional, infectious, physical and chemical, specific sensitivities, and emotional factors. He rather emphasizes the emotional factors, tending to belittle the specific sensitivities and the value of hyposensitization, and, under the discussion of prognosis, implies that a great many of these children recover without treatment.

Joos and Ellis[133] report a follow-up study of one hundred children under twelve years of age with asthma who were followed for three to ten years. Bacterial sensitivity was the principal cause of asthma in this series. Eighty-three of the children gave reactions to bacteria on skin tests, and in forty-four of these children the asthma attack was provoked by an upper respiratory infection. The entire program, including hyposensitization measures, gave favorable results in 61 per cent of the cases.

Blumstein[26] describes the diagnosis of asthma in childhood and emphasizes that a complete study is required if they are to be treated properly.

Tuft,[251] on the basis of his experience at the Jewish National Home for Asthmatic Children at Denver, feels that intractable asthma in childhood, such as would require admission to this home, will improve usually within a few days of the children's arrival at the home. He feels the causative factor for the improvement is removal from the parents; therefore, emotional upsets in the home are factors which should seriously be considered in asthma in children, particularly those who fail to respond to therapy.

Hallowitz[106] also recommends institutionalizing asthmatic children who are very severe and chronic, and feels the improvement results from separation from the family.

Ehrlich et al[75] present a complete review of the subject of status asthmaticus in infancy and childhood, describing the treatment in detail with emphasis on the importance of intermittent positive pressure breathing of the inspiratory type. They describe in detail the type of machines which are recommended and the methods by which they should be used.

Goddard and Roorbach[99] also recommended intermittent positive pressure breathing. Over a period of four years they treated one hundred children with asthma by intermittent positive pressure breathing aerosol therapy, the medications consisting of bronchodilators, antibiotics, Alevaire, and in some cases crystalline trypsin. These children were treated for their asthma in other ways, such as, by hyposensitization, bacterial

vaccine, etc. Forty of these 100 children had failed to respond to usual methods of therapy which had been found quite adequate for another 105 children with less severe asthma, and in the series of one hundred cases, 98 per cent of the children were very definitely helped by this type of therapy. They believe, therefore, that it is an important adjunct in treatment.

Prickman,[194] Overall,[188] MacPherson,[159] and Bernstein and Klotz[17] all discuss in some detail the treatment of asthma.

Bendkowski[15] describes the use of methylpentynol in the treatment of asthma where there are frequent nocturnal attacks. This drug is a hypnotic with no antispasmodic action. It is a nonbarbiturate and is strongly contraindicated if barbiturates are being given to the same patient. It has no undesirable side effects. The drug was given to fifteen patients who were under treatment for asthma with frequent nocturnal attacks, with fifteen controls, and at the time of the experiment the author did not know which patient was receiving the drug and which was receiving the placebo. The drug was found to be highly effective in giving these patients a restful night's sleep.

Howell[126] recommends bronchoscopy for severe asthmatics who are responding poorly to treatment. This has the value of removing mucus, finding bronchostrictures of inflammatory origin and also for obtaining bacteria for autogenous vaccine for hyposensitization. It is also valuable for observing other diseases such as bronchiectasis which can cause wheezing.

Dorinson[69] emphasized the value of breathing exercises for bronchial asthma and pulmonary emphysema. He describes in detail how they should be carried out.

This is a procedure which is probably not used enough in this continent, although it has high favour in England. It is very important to know, however, that it is an adjunctive treatment of asthma and in no way does it replace hyposensitization, drug therapy, etc.

Shuey and Grater[227] treated twenty-three patients, both children and adults, with long term antibiotics. These patients had repeated respiratory infections which seemed to precipitate their asthma. The treatment was continued for periods ranging from three to eighteen months. Of the twenty-three patients, sixteen obtained excellent results, four moderate improvement, two showed slight improvement and one no improvement.

This treatment, of course, is very useful in those patients who have repeated upper respiratory infections which precipitate their asthmatic attacks. Most of these children, however, are also allergic to non-bacterial allergens, particularly the inhalants, and it is essential that they be hyposensitized with these after adequate investigation and skin testing. The treatment and prevention of the infections is important but not the whole story.

Tuft and Ermilio[253] gave asthmatic children, over a course of several

years, 2,036 injections of bacterial vaccine all by the intracutaneous method. They concluded that the intracutaneous method of vaccine administration has a definite advantage in that the incidence of local reactions was only 3.8 per cent, and only 0.24 per cent were of sufficient severity to cause great discomfort. With the use of subcutaneous bacterial vaccine the incidence of reactions is much higher. Because of the fact that these patients are under other methods of treatment, including specific hyposensitization, they could not evaluate how much good the bacterial vaccine did their patients.

Frankland et al,[86] in a controlled study, evaluated the value of autogenous bacterial vaccine in the treatment of asthma. There were two groups of patients, each looked after by a different physician, with a total of one hundred patients receiving the vaccine and eighty-four controls receiving only a carbol saline solution. All of these patients were receiving standard methods of treatment also. In the vaccine group, 58 per cent showed improvement, and in the control group, 52 per cent showed improvement. Therefore, they conclude from this study that autogenous bacterial vaccine was of no greater benefit to the patient than injections of carbol saline.

The objection to this experiment, although it was carefully carried out, is that it is very difficult to evaluate beforehand just how great is the role of bacterial allergy in causing the asthma. These patients were receiving other methods of treatment, and, of course, if most of their asthma was due to inhalant sensitivity and other non-bacterial factors the value of bacterial vaccine would be obscured in such a study. In selected cases it is unquestionably true that bacterial vaccine is of considerable value.

Longacre[151] has written a general discussion on the use of antibacterial therapy in infectious asthma. He points out that this type of therapy is much more useful for those in whom each asthmatic attack is dependent upon a new and acute infection than in the more chronic asthma where infection precipitates some attacks but attacks are also precipitated by other factors.

Tainter et al,[240] in a discussion of Alevaire, present evidence based on *in vitro* experiments to show that Alevaire is the logical agent to be applied as a detergent in the tracheobronchial tree in respiratory infections. The authors showed that the surface tension of the sputum was remarkably lowered by the addition of this agent so that the mucus could be separated from the mucosa and coughed up. It should be pointed out, however, that this agent must be used carefully, particularly in small infants, because if it is used in an excessive amount it can produce so much loose tracheabronchial secretion that the patient can literally drown in his own secretions. Therefore, it should be given intermittently and the patient observed while under this form of treatment.

Miller et al[175] report on the use of Alevaire inhalation in asthma, sinus-

itis, bronchitis and bronchiectasis in adults. Seventeen adults suffering from one or more of these conditions received the Alevaire by one of two routes. One was an open top tent method for overnight therapy and the other a direct application of a nebulizer equipped with a nasal tip to the external nares for short periods of therapy. They found the medication extremely helpful in all of these conditions for thinning out the secretions so that they can be eliminated from the body and report they have had very excellent results with this drug for similar conditions in children.

Rapaport et al[197] have made an initial report on the use of an electrical pneumotachograph, a device for recording the instantaneous linear time rate of change in the ventilation of the lung on a group of one hundred children from four to fourteen years of age. They discuss the normal pattern of respiratory exchange and the type found in the asthmatic child with flattening of the expiratory phase. They believe this investigation shows that this instrument will be of value in the differential diagnosis of asthma in children and in those patients with repeated episodes of pulmonary infection accompanied by wheezing. They feel the prognosis of asthma in children under treatment who have normal curves between attacks is more favorable than in those children where the curves remain unchanged between attacks.

Rakower et al[196] review the literature on massive atelectasis occurring during attacks of asthma. They state that only fifteen cases have been reported, ten in children and five in adults and add two more cases, both children. They discuss the etiology and diagnostic criteria. Treatment consists of postural drainage, expectorants, trypsin and aerosol inhalation. Antibiotics are also necessary. Small areas of atelectasis in asthma are extremely common and it is very likely that there have been a great many cases of massive atelectasis which have occurred and not been reported. If the patient is in danger of his life or if there is not rapid enough clearing of this condition, bronchoscopic suction would appear to be the treatment of choice.

Holman[123] reports two cases of patients with foreign bodies in the lungs which gave asthmatic symptoms. In one, two bronchoscopic examinations were negative before the foreign body was found. Both patients had bilateral rales. In both patients the asthmatic wheeze was relieved by removal of the foreign body.

Foreign bodies as the cause of asthmatic symptoms are not at all rare and are something all allergists, particularly those dealing with children, should be on the lookout for. The history of choking at anytime, the presence of signs more marked on one side than on the other, or an area of consolidation in the lung which does not clear, all should make one very suspicious of a foreign body as a cause of the wheezing.

Fein[78] reported the case of a seven-year-old child with asthma who

appeared to be a typical asthmatic except that she gave only mild reactions to house dust and to pollens. Hyposensitization with house dust and symptomatic treatment were of very little help. To rule out foreign body or bronchiectasis, a bronchoscopy was done and the secretion revealed pseudomonas aeroginosa in pure culture. Sensitivity studies on this organism showed it to be sensitive to chloromycetin and polymyxin B and after treatment with these drugs the wheezing cleared and she remained symptom-free for the following twenty-two months. It was concluded, therefore, that the asthma was due to this organism present in pure culture in the bronchial tree.

A case like this, which will clear up entirely when the infecting organism is removed, must be quite unusual. However, it is very common for asthmatic symptoms, particularly in chronic cases, to be prolonged indefinitely because of infection in the tracheobronchial tree; therefore, in the chronic cases, at least, throat cultures and possibly cultures from bronchoscopic suctions should be done and the appropriate antibiotics given.

Dekker and Groen[62] studied the mechanism of wheezing in asthma. They postulated that it may be produced at least partially by a narrowing of the trachea and larger bronchi. They feel this is caused by the positive pressure created in the thorax by the contraction of the abdominal, thoracic and cervical musculature during the typical asthmatic inspiration. To demonstrate this they taught both healthy people and asthmatic patients to wheeze, and in both sets of subjects the wheezing was very similar to that heard in the spontaneous asthmatic attack. By special x-ray techniques they showed changes in the diameter of the trachea and main bronchi during inspiration and during voluntary wheezing expiration in both sets of subjects and also did similar studies on asthmatic patients during spontaneous attacks. They demonstrated narrowing of the lumen of the trachea extending into the lower part of the cervical trachea and did similar studies on isolated human lungs obtained at autopsy. In all patients and in the isolated human lung they demonstrated the narrowing of the cervical and thoracic trachea and they suggest that this is part of the mechanism by which asthmatic attacks are brought about.

Tuft[250] studied the serum of 121 asthmatic children by paper electrophoresis and showed there was a lowered albumin and elevated alpha 2 and gamma globulin. Patients whose asthma had not occurred for thirty-one days showed only the albumin and gamma globulin changes. Steroids increased the albumin and the alpha globulin but exerted no effect on the previously elevated alpha 2 globulin and decreased the gamma globulin levels towards normal. In thirteen cases an unusual electrophoretic fraction in the alpha 2 beta area was encountered.

Derbes et al[64] report that in thirty-three of their sixty-eight patients with fibrocystic disease of the pancreas, asthmatic findings were prominent.

They feel that the wheezing is due to a combination of bronchospasm, edema of the bronchial mucous membranes and retention of excessive mucus, and emphasize that this disease should be excluded whenever bronchial asthma is a conspicuous feature in young patients.

This observation is so important that infants and small children who are suffering from asthma, particularly if they are having repeated attacks or are having chronic wheezing, should have their sweat electrolytes done as part of their investigation.

Glaser and Smelzer[98] reported 389 children ten years of age or less who suffered from bronchial asthma. Of these, 320 (82 per cent) showed prodromal symptoms of the asthmatic attack, consisting in most cases of respiratory symptoms, such as, nasal discharge, coughing, sneezing, and nasal obstruction and, in some cases nonrespiratory symptoms—chiefly ocular symptoms. If the child had prodromal symptoms, regardless of their nature, the parents were instructed to give immediately at the onset of the symptoms three medications—an antihistamine, nose drops and a cough medicine. They were also to put the child in a dust-free room, give him an aminophylline suppository every night at bedtime and every twelve hours thereafter until the danger of an attack had passed, and, in cases where these measures were not effective, they were also to give the child an antibiotic. Of the 320 children, adequate treatment and follow-up was carried out in 174, and there were satisfactory results in 168 (96.4 per cent). Satisfactory results were defined as complete abortion of the asthmatic attack or very significant decrease in severity and duration. This procedure, therefore, is recommended in all cases of children with asthma who suffer from prodromal symptoms.

Watson[264] reviewed twenty patients on whom an initial diagnosis of asthmatic bronchitis was made and in no case was this diagnosis applied to any children who had an allergic background or other allergic stigmata, such as, eczema, urticaria, etc. Most of the patients were less than a year old. Of these twenty children during a follow-up averaging five years in length, eight developed asthma. Five additional patients were considered to be mildly allergic because of upper repiratory tract infections and wheezing. One child had developed eczema, while another had developed a rather severe drug sensitivity. Another had developed contact dermatitis. In two other patients their siblings had developed major allergy and, therefore, in only two cases had the children or their siblings failed to show any allergic stigmata up to the time of follow-up.

The implication of this study is that most of these children suffering from so-called asthmatic bronchitis are allergic.

It is the experience of all practicing pediatricians that there are large groups of children, especially infants who suffer from respiratory infections associated with wheezing, in whom it is very difficult to say at the time of the first or even second illness whether they are suffering from asthma or not. These children should be carefully followed and

if they continue to have the wheezing bouts should tentatively be treated as asthmatics, as has been pointed out previously in Buffum's paper. However, it is equally important not to misdiagnose them definitely as asthma before the proper criteria, as were pointed out by Buffum, have been fulfilled.

Two reviews have appeared—one by Glaser[95] covers the subject of asthma in detail in children, and the other by Gottlieb[102] reviews the literature on bronchial asthma published during 1954.

STEROIDS IN ASTHMA

Savidge and Brockbank[218] report on two patients suffering from severe bronchial asthma who while under treatment with oral cortisone died. Including these two, there are eleven patients with severe bronchial asthma who died either while receiving cortisone or ACTH. All were adults. They do not feel that they can come to a definite conclusion as to whether the asthma or the drug killed the patients but such deaths are usually attributed to asthma, and they do not feel that the steroid can be definitely exonerated.

Several papers have appeared on the use of the steroids in the treatment of asthma. The use of ACTH, cortisone and hydrocortisone are described by Baldwin et al,[12] Pearson,[189] Davies and Williams,[59] MacLaren and Frank,[158] and by Walton.[262] Walton also discusses the use of meticorten and meticortelone. All of these authors found the drugs quite effective for the relief of symptoms, but stress the dangers of these drugs and also the need for overall management of these patients by standard anti-allergic treatment. Several papers have also appeared on the use of prednisone in the treatment of asthma. Papers by Arbesman and Ehrenreich,[7] Skaggs et al,[231] Schwartz,[220] Barach et al,[13] Jenkins,[130] and Seigel et al[229] describe many cases of asthma, usually chronic, treated with meticorten. All of them agree that the side-effects are less serious than with the older steroids but that they are still important enough to be watched. Arbesman and Ehrenreich also used nine alpha fluorohydrocortisone in the treatment of asthma and found it to be of no value at all.

Schwartz[220] describes the use of prednisone in one case of diabetes mellitus with asthma and found it much safer than the older steroids because of the much less marked effect on the blood sugar, and, therefore, less insulin was required to control the patient.

Foulds et al[84] describe the use of hydrocortisone in the treatment of allergic adjunctivitis, allergic rhinitis, bronchial asthma, all by topical application. The allergic conjunctivitis was treated with drops of solution, the allergic rhinitis by inhalation of the powder into the nose and the bronchial asthma by inhalation into the lung. Most cases showed considerable improvement.

Gregoire[104] reported on three patients with pulmonary tuberculosis and

asthma who did not respond to the standard methods of treatment but required ACTH. This was found to be safe therapy in doses not exceeding 20 units a day, without tubercular spread, provided the patient received streptomycin, PAS and isoniazid. There was no reactivation even in cases where it was given for more than a year.

Kennedy and Thursby-Pelham[137] report twelve asthmatic children, studied in detail by evaluating the respiratory function by means of the expiratory flow rate (EFR) over the first 0.75 seconds of expiration. They feel this is a valid and practical method for assessment of children with asthma. These children had this measurement carried out a great many times before treatment and also after the inhalation of 1:1,000 adrenaline. Half of them were given cortisone in doses of 75 mgm daily for three weeks and 50 mgm daily for another two weeks, while the other half received placebo. Then the series was reversed, the placebo group receiving the cortisone and the cortisone group receiving the placebo. The adrenaline produced an overall increase in the EFR of 13 per cent. On an average, the cortisone also produced a 13 per cent improvement. The placebo produced no improvement. Treatment of the children by cortisone plus adrenaline inhalation produced an overall improvement in the EFR of 28 per cent.

HAY FEVER

Two papers have appeared on the topical use of hydrocortisone alcohol in the treatment of hay fever. Tuft[249] reported twenty-five patients who were treated with hydrocortisone alcohol combined with two vasoconstrictors used locally in the nose. Twenty of the twenty-five showed significant objective improvement in the appearance of the nasal mucosa and nineteen of the twenty-five had marked subjective relief. Pennypacker,[190] in a similar study on twenty-three patients, showed an objective improvement of the nasal membranes in fourteen of twenty patients examined and long term benefit in fourteen of the twenty-three patients symptomatically. Both these authors conclude that the material is a valuable adjunct in the treatment of ragweed hay fever.

Herxheimer and McAllen[119] reported the use of hydrocortisone snuff in twenty-four patients with severe hay fever. In many cases it was necessary to use a vasoconstrictor to unblock the airway first. All patients but one obtained excellent relief within ten days and most responded dramatically within forty-eight hours. Four of the ten with asthma did not have any asthma while under this treatment.

Godfrey et al[100] reported the use of prednisolone snuff in eighteen patients with hay fever and a placebo snuff in twenty controls. Treatment was given for one month during the hay fever season and only 2 mgm of the drug was required daily. It was of considerable value in control of both the nasal and eye symptoms and no side effects were observed.

Kaplan et al[136] give a very comprehensive review of the literature on hay fever over a two year period.

ALLERGY OF THE EAR, NOSE AND THROAT

Sanders[217] discusses the question of persistent nasal symptoms in children, pointing out the difficulties of telling whether they are due to allergy, to infection or both and the necessity for a clear differentiation before procedures like removal of tonsils and adenoids are carried out.

One cannot help but take exception to his statement that skin tests need be performed only to confirm suspicion of sensitivity since skin tests are performed only to determine the responsible allergens causing the symptoms once a diagnosis of nasal allergy has been made. The nasal smear is very helpful as a laboratory aid in this diagnosis. He also states that skin tests are not reliable in infants, a statement with which a great many allergists would not agree.

Treynor[248] presents a complete review of the subject of allergic vasomotor rhinitis or perennial allergic rhinitis covering it in all its aspects.

Dunn[70] studied twenty-five patients with allergic rhinitis who were placed on the usual anti-allergic therapy and followed for six months by means of nasal smears. With treatment the eosinophiles were eventually replaced by leukocytes, but in spite of this symptoms persisted. Then treatment with an antibiotic nasal spray cleared the symptoms, although symptoms returned when the use of the spray was discontinued. A similar spray with hydrocortisone in it also produced more rapid clearing.

Surber[238] reports sixty-five cases with chronic bacterial allergy of the paranasal sinuses. He feels that most of them should be treated medically from an allergic point of view plus the use of antibiotics. Fifteen who were treated without immunization or desensitization did not do well, but the group treated with autogenous vaccine did better. Most severe cases do require surgery and sometimes require radical surgical procedures without destruction of functional tissues.

Hampsey[111] discusses allergic sinusitis in children, pointing out that clinical examination and examination of the secretion under the microscope are more important than history in children. He emphasizes that a great deal can be done on these children to prevent them going on to chronic sinus disease and that the child with frequent colds who is allergic usually responds very well to treatment.

Derlacki[65] believes that food sensitization is an important cause of perennial nasal allergy, being an important factor in approximately 25 per cent of his cases. While inhalants tend to produce paroxysmal sneezing, intermittent nasal blocking and watery discharge, foods tend to produce a more continuous obstruction and a copious mucoid discharge. His method of investigation is to put the patient on a basic diet consisting of foods of very low allergenicity and then give feedings of other

foods, comparing the symptoms in the nose before and after feedings to see whether or not a given food can be implicated.

Craft[57] stresses very emphatically that allergy of the nose is often the cause for symptoms which are attributed to tonsils and adenoids and that before any patient is operated on for these he should be screened as to whether or not he is allergic and, if so, any operation should be left until his allergy has been treated.

Elkins[76] discusses allergy at the external ear, middle ear and internal ear and gives illustrative case reports. He points out that many of these conditions may be entirely or partly allergic in origin. He feels this is common enough that any ear condition not responding to customary otologic therapy or continuing to recur frequently should be further investigated from an allergic standpoint. He finds that allergic manifestations in the ear respond as completely and as rapidly to adequate allergic management as do allergic manifestations in other areas.

Two reviews on this subject have been written. Rinkel et al[206] cover the whole field of allergy of the ear, including diagnosis and treatment, and Vaughan[258] covers allergic problems in the upper respiratory tract in children, including rhinitis and sinusitis, recurrent laryngitis and allergy of the ear.

MISCELLANEOUS RESPIRATORY ALLERGY

Herlitz[117] studied 211 children with chronic upper respiratory infections which were not clearly pure infections or pure allergy who had no history of asthma or hay fever. He found an incidence of 23.6 per cent allergic members in their families as compared to 6.1 per cent in the families of 105 controls who did not suffer from chronic upper respiratory infections. Forty-five of these 211 children had suffered from cutaneous allergy, but when the remaining 166 alone were considered, the incidence of allergy in the parents and siblings was found to be essentially the same. These two groups were essentially the same age, sex, size of family and social circumstance, and siblings were not included in either group.

Glaser[93] divides the children who suffer from frequently recurring or even apparently continuous upper respiratory infections into two groups. The first group consists of those who have recurrent upper respiratory infections. This is extremely common in allergic children, and the episodes must be differentiated from the common cold, sinusitis, rhinitis, nasopharyngitis, laryngitis, tracheitis, and bronchitis. There is listed in table form the differences between the allergic and infectious conditions of the upper respiratory tract, and this is a very valuable table. The diagnosis is confirmed by the finding of eosinophiles in the nasal smear. Usually the diagnosis can be made on history alone if the complaint is that the child has one cold after another or colds all year long or all winter long, as opposed to the non-allergic child who may have two or

three colds in the winter separated by good health. The second condition is perennial allergic rhinitis which occurs with almost identical frequency and often in association with recurrent upper respiratory infections. It is often easily diagnosed by history alone, the complaint being that the child has a cold all the time. This may be complicated by seasonal allergic rhinitis due to pollens. Recurrent upper respiratory tract infections are not infrequently a precursor of bronchial asthma but this is less true of perennial allergic rhinitis. Both may lead to complications of infection in the upper respiratory tract. The perennial allergic rhinitis is much more resistant to treatment than the recurrent respiratory infections, but it is important to treat them from an allergic point of view because of the danger of bronchial asthma following. Treatment is described in detail.

Hosen and Carabelle[124] studied 227 cases of non-febrile upper respiratory infections in children under two years of age by means of microscopic examination of the nasal secretions, cultures and sensitivity tests of the organisms. They made a similar study on 175 patients over two years of age and into adult life. In an effort to make some appraisal as to the relationship of allergy to bacterial infection they found that infection is much more frequent in allergic respiratory episodes in patients under two years of age than in the older group and favorable results are obtained by the specific use of antibiotics in allergic conditions complicated by infection. They feel that infection is an important secondary factor which acts as a trigger mechanism to precipitate or aggravate an existing allergy.

Collins-Williams[53] presents a summary of the diagnosis and treatment of respiratory allergy in children.

FURTHER OBSERVATIONS ON STEROID THERAPY

Lipman[146] reports a series of 417 patients with various allergic disorders, chiefly respiratory and dermal, who were treated with steroid hormones by various routes. Sixty-eight per cent showed a good response, 19 per cent a fair response and the remainder poor or unsatisfactory results. There were side reactions in 8 per cent with recovery in all when the treatment stopped. He stresses that these drugs are only for symptomatic therapy and do not replace allergic management. Parenteral ACTH was the drug of choice in 95 per cent of the cases.

Levin[143] reviews his experience in treating approximately 200 with ACTH, cortisone and hydrocortisone. Most of these patients had bronchial asthma but some had dermal allergy. He also discusses allergic reactions to ACTH and the steroids, pointing out that many have been reported, including several cases of fatal anaphylactic shock from ACTH, but so far no such allergic reactions have been reported in children. He reports two patients of his own who had acute reactions to ACTH, but this was proven to be due to the gelatin base and not to the ACTH

itself. He also reports one case in which the patient suffered from asthma presumably due to hydrocortisone itself in nose drops.

Collins-Williams[52] discusses the use of ACTH and cortisone in allergic children. The principles for the use of these drugs are as follows: (1) The drug should definitely not be used where standard methods of symptomatic relief are effective. (2) The drug should not in any way be used to replace accepted methods of anti-allergic therapy. (3) The parents should be warned that the drugs give temporary and symptomatic relief only. (4) The lowest dosage possible to obtain a reasonable amount of relief should always be used. (5) The drug should never be stopped quickly, particularly if used in large dosage. (6) If the patient has received cortisone and requires an anesthetic, cortisone should be increased or re-started if it has been discontinued.

There are three indications for the use of these drugs in asthma: (1) for the treatment of the acute attack, especially status asthmaticus; (2) for the long-term management of a patient with very severe symptoms while waiting for the accepted anti-allergic therapy to become effective; and (3) in the rare patient who does not respond to anti-allergic therapy.

Four indications for the use of the drug in eczema are given: (1) to control the severe exacerbation of the disease which is causing a great deal of distress to the patient; (2) to give the patient a reasonable amount of relief while waiting for the orthodox methods of treatment to become effective; (3) to clear the skin temporarily so that skin testing can be done; and (4) to treat exceptionally severe cases which have not responded to the usual methods of treatment.

Brown and Seideman[37] report the use of prednisone and prednisolone in sixty-four patients with bronchial asthma, thirty-eight with allergic dermatoses, seventy-nine with seasonal allergic rhinitis and nine with perennial allergic rhinitis. Their results were good.

Grater[103] reports the use of intravenous hydrocortisone for the control of the acute asthmatic attack in six patients. Progress was followed by means of respiratory function studies. The author concludes that the infusion of from 100 to 300 mgm of intravenous hydrocortisone over a six-hour period has a definite beneficial effect.

Three papers have appeared on the relationship of steroid therapy to infection. Smith and Cleve[232] report four cases, all of whom suffered from severe infectious complications while on cortisone therapy, with three deaths. They stress that the danger of infection during cortisone therapy must be seriously considered in all patients who receive these drugs.

Shaper and Dyson[223] report on two patients, both adults, who while on therapeutic doses of cortisone developed fatal staphylococcal septicemia. They discuss the dangers of such infections in patients treated with cortisone and ACTH and cite experimental evidence on animals to show that the use of the growth factor in such patients may counteract the

effect of corticotrophin or cortisone to lead to serious and sometimes fatal infections.

These two papers stand as a warning about one of the great dangers of steroid therapy and emphasize that it should be used only when there is real need for it.

Long,[150] in a study of the influence of steroids on the immune responses to bacterial infections, divides animal organisms into two groups. The first group, consisting of rats, mice, rabbits, and ferrets, were found to be so-called cortisone-sensitive, that is, they were unable to maintain body weight, gamma globulin synthesis and antibody production under cortisone administration and their resistance to bacterial infection was therefore depressed or abolished. On the other hand, the Rhesus monkey, guinea pig and man were classed as cortisone resistant because they could maintain body weight, gamma globulin synthesis and antibody production under cortisone administration, and, therefore, their resistance to bacterial infection is not significantly affected. This paper draws attention to the fact that it is difficult to translate results of animal experiments to man with regard to the effect of steroids on infections.

Siegel et al[230] made 152 determinations of the plasma 17-hydroxycorticosteroid levels on fifty-seven asthmatic and thirty-two normal children. In the asthmatics the levels were determined at four stages of the disease, namely, asymptomatic, mild, moderate, and severe. In those patients with moderate or severe symptoms the plasma levels were significantly higher than in the asymptomatic or mild groups, or in the control group, and in the mild or asymptomatic cases the levels were not statistically different to those of normal controls. Fifty-seven plasma 17-hydroxycorticosteroid levels in twenty-one allergic children receiving prednisone and prednisolone were also measured and found to correlate statistically directly with the amount of drug being administered, but no critical hormone level at which the majority of patients became asymptomatic could be determined.

Segaloff[222] reviews the deleterious effects of cortisone and ACTH and stresses that it should be assumed that patients who have had sufficient steroid therapy to produce signs and symptoms of hypercorticism have atrophic adrenals for at least one year after cessation of therapy, and, therefore, if these individuals have to go through a period of stress such as an operation, hormones should be restarted a couple of days prior to the operation and continued into the post-operative period.

Blodgett et al[24] have contributed important data on the effect of cortisone therapy on growth in children. They studied several types of patients but only the allergic patients who were endocrine normal will be discussed here. There were twenty such patients who received therapy on an average of 14.5 months with a range of three to twenty-five months. They were carefully studied by measurements of height, weight, x-rays of the wrist and of the hands for bone age. The cortisone was administered

orally, the total daily dose being divided into two or three portions. All cortisone dosages were expressed as per square meter of body surface area for twenty-four hours. By making growth curves it was observed that when the dosage of cortisone was at certain levels, growth was markedly reduced and when this level was reduced sufficiently there were striking growth spurts. These observations, of change in growth rate after institution and then withdrawal of cortisone, could be detected within a few weeks of a change in the dose of the drug. In other words, it was not necessary to eliminate cortisone therapy altogether to make it possible for a patient to undergo a compensatory growth spurt. It was found in the endocrine-normal patients that a minimum of 45 mgm per square meter per day was required to reduce the growth rate. They conclude tentatively that cortisone can be administered to growing children over a considerable period without necessarily altering the child's potential ultimate stature, but that it is particularly important in the endocrine-normal children to reduce dosages below growth-suppressing levels from time to time to permit a gain of lost ground during intervals of relatively heavy doses before the age when there is closure of the skeletal epiphyses.

This data is extremely important for allergists who are keeping allergic children on cortisone for a long period of time. The importance of the data becomes more evident if the dosage 45 mgm per square meter per day is transposed to daily dosages for various ages. Considering children of normal height and weight for each age, the growth depressing dose in mgm per day is as follows: birth— 9 mgm; one year, 19 mgm; two years, 24 mgm; three years, 27 mgm; four years, 30 mgm; five years, 33 mgm; six years, 36 mgm; seven years, 38 mgm; eight years, 40 mgm; nine years, 44 mgm; ten years, 47 mgm; eleven years, 51 mgm; twelve years, 54 mgm; thirteen years, 57 mgm; and fourteen years, 60 mgm. In other words practically all allergic children who are put on cortisone preparations receive growth-depressing doses.

Hill[120] made similar observations. He followed the growth and height of forty-three allergic children, from six months to twelve years of age, who were treated with cortisone for periods varying from three to thirty months. No child was given more than 75 mgm a day and only one received as much as this for longer than ten days. The usual maintenance dose varied from 25 to 50 mgm per day. Twenty-four children gained in height below the average rate and fifteen above the average rate, and four the same as the average. From a practical point it appears from the data that such a decrease in growth, if present, is not sufficient to make any difference in deciding whether or not to use the drug. These observations, of course, apply to rather small doses for short periods of time and are quite a different set of observations from those of Blodgett et al.

Baar and Wolff[8] report two children, one suffering from asthma and the other from dermatomyositis, who were treated with cortisone and died from pancreatic necrosis or acute hemorrhagic pancreatitis. No other

cause could be found for this complication and in each case it was assumed that the pancreatitis was a result of the cortisone therapy. They could find no similar reports in the literature, although there are reports of pancreatic lesions being produced in rabbits on intramuscular cortisone. They feel that the descriptions of the experimental pancreatic necrosis and findings of their two cases differ only in severity.

Bonner and Homburger[28] report an adult with atopic dermatitis who was treated with prednisone and developed a very severe generalized erythematous dermatitis of bullous type which was due to the prednisone. This sensitivity reaction could be reversed by the combination of hydrocortisone and ACTH which also controlled the original dermatitis. They say this is the first such case reported, although skin rashes due to prednisone have been reported previously in five of eleven children who received the drug for a long time for rheumatic fever.

Good et al[101] have written an exhaustive review on the untoward reactions to therapy with cortisone and other steroids in pediatric practice. There were 340 children who received ACTH and cortisone for various diseases and in these children, there were 10 per cent serious reactions, including disturbances in fluid and electrolyte equilibrium; central nervous system manifestations including thrombosis, seizures, hypertensive encephalopathy, psychotic reactions; gastrointestinal disturbances including hemorrhage and perforation; infectious diseases like septicemia, cellulitis, herpes zoster infections, sterile peritonitis, silent pneumonia, empyema, meningitis and arthritis; skeletal manifestations, including pathological fractures and miscellaneous complications including unexplained sudden death and insulin resistant diabetes mellitus. The authors did not observe any complications of chicken pox infections but refer to the twelve fatal cases of chicken pox in cortisone-treated children which have been reported. They also report potential hazards of adrenal hormone therapy, such as, carcinogenic effects, possible effects of high serum cholesterol, the possibility of producing wide spread hemorrhagic necrosis and possible disturbances in nucleic acid metabolism.

Eisenstadt and Cohen[74] review the literature on osteoporosis from prolonged steroid therapy and report two more cases, both in adults, who on prolonged therapy with cortisone and ACTH showed osteoporosis. They recommend periodic x-rays of the spine and urinary calcium excretion studies. In a review of the literature they point out that this has been reported once in a child—a nine year old boy—who was on steroid therapy for rheumatoid arthritis.

Henneman et al[116] report the clinical symptoms following the abrupt cessation of cortisone therapy in nineteen patients with chronic asthma. These were all adults who had been receiving cortisone in rather large doses for prolonged periods. Following abrupt cessation of therapy within twenty-four hours nearly all the patients developed headache, nausea, vomiting, restlessness and muscle and joint pain. These symptoms sub-

sided spontaneously after two to five days. In general, the longer the period of cortisone therapy the more severe were the symptoms, but the severity or duration of the withdrawal symptoms bore no evident relationship to the size of the dose of cortisone. They discuss the mechanism of these reactions.

PENICILLIN ALLERGY

Papers on acute, fatal and non fatal, reactions to penicillin are appearing in increasing numbers. Anderson[5] reports a child who after an injection of penicillin had a very severe atypical serum sickness-like reaction. Still[236] reports an adult who had a severe penicillin reaction manifested as an acute abdominal emergency which required laparotomy. Campbell[45] reports an adult who had a fatal anaphylactic reaction following an intramuscular injection. Tidswell[246] reports four cases of non-fatal anaphylactic shock following injection of penicillin. Calvert[44] reports an adult who had an almost fatal anaphylactic reaction from penicillin. MacGibbon[157] reports an adult who had a very acute reaction with recovery. Lang and Clagett[140] report an adult with an acute anaphylactic reaction following oral penicillin. Bierlein[19] reports an adult who had an acute anaphylactic reaction following an intracutaneous skin test with penicillin containing only 0.000003 units of penicillin. Winton and Nora[271] report fatal anaphylactic shock to penicillin in an adult following intramuscular therapy and also report several cases of rashes following the use of penicillin.

Maganzini[160] reports two cases of severe reaction to penicillin administered orally. He summarized the English language literature and found a total of thirteen cases of anaphylaxis to penicillin administered orally due to tablets and two more due to lozenges. In his own two cases skin tests were not done but the passive transfer tests were negative. Bell[14] reports one case of acute anaphylactic shock to oral penicillin and another case of a severe reaction to oral penicillin, both in adults. Mason[165] reports a two-year-old child who had a fatal reaction following one dose of oral penicillin.

Peters et al[193] report three patients who had non-fatal anaphylactic reactions following oral penicillin and one fatal case following intramuscular penicillin. By means of direct skin testing and passive transfer tests they demonstrated the presence of a heat labile circulating antibody which they believe can be used for detecting potential future anaphylactic cases. They discuss the limitations of penicillin skin tests but feel that skin tests should be done on atopic individuals and if the tests are positive the use of penicillin should be avoided. Lewis[144] discusses the prevention and treatment of acute immediate reactions to penicillin. Editorially[71] the British Medical Journal warns against the danger of penicillin.

Lapin[141] reviews the literature on allergic reactions to penicillin. Reports of severe anaphylactic reactions are becoming more common. In 1951 he

could find no reports of severe anaphylactic reactions in children. In 1952 there were only two reports. In 1953 and 1954 there were a total of 149 reactions reported, 136 in adults with sixty-one fatalities, and thirteen in children with six fatalities. However, of these 149, forty-two were due to Neo-Penil, leaving only 107 due to the conventional forms of penicillin—ninety-nine adults with forty-three fatalities and fifty-six near fatalities and eight children with four fatalities and four near fatalities. In other words, this type of reaction is still rare in children under thirteen years of age, at the time of this report. On the basis of these figures, he feels that it is good procedure to use penicillin for the prophylaxis of complications of respiratory infections in children. In a series of 402 children from three months to ten years of age seen in private practice who were given oral penicillin in large doses at the onset of respiratory infections, there were no complications to the infection and there were only 0.5 per cent mild urticarial reactions with no major reactions as complications of the penicillin therapy. He therefore concludes that oral penicillin can be used routinely in an effort to avoid the complications of upper respiratory infections in infants and children.

Editorially, the ANNALS OF ALLERGY[72] points out that Dr. Lapin's conclusions are not shared by all pediatricians and pediatric allergists. Many feel that mild infections in children can be cleared up without any antibiotics at all and that for more severe infections one should use one of the other antibiotics which can be given orally, reserving penicillin either to treat complications or for more severe infections where it is required to be given intramuscularly. This remark, of course, does not apply to a child who has suffered from rheumatic fever or nephritis where the use of penicillin for even very minimal respiratory infections is justified, in view of the fact that the major disease may be flared up again and serious illness caused by even a very mild streptococcal infection.

Matheson and Elegant[167] studied a group of children with skin tests to penicillin. In a group of 391 who had received penicillin injections on many occasions, 390 did not demonstrate any skin sensitivity to penicillin. Approximately 4 per cent of this group had vague histories of serum sickness-type reactions following penicillin injections. On the other hand, in a group of six children who had experienced severe constitutional reactions following the administration of penicillin, five gave immediate positive skin tests to penicillin. In two, passive transfer tests were positive with penicillin. The authors conclude that an immediate positive skin test to penicillin in children who have had penicillin contact indicates potential clinical sensitization but on the other hand negative skin tests with penicillin do not rule out potential anaphylactic-like reactions.

Tuft et al[255] did penicillin skin tests on three groups of patients. Group one consisted of 134 individuals who had never received penicillin. Group two consisted of 463 individuals who had a history of penicillin without any reaction. Group three consisted of thirty-two individuals

who had received penicillin followed by reactions. The tests were done by the scratch method, by the intracutaneous method, with the vehicles which contained the penicillin and in some cases by patch test. In group one there was one positive reaction, in group two, nine positive reactions with penicillin, and in group three, three positive reactions. Thus, in 629 patients there were thirteen positive reactions but three of these also gave reactions with vehicles, and therefore, there were only ten significant positive reactions, an incidence of 1.8 per cent. The incidence of specific positive reactions in group two was 1.3 per cent and in group three, 9.4 per cent. They found that the reactions were much more apt to be positive if the test was done shortly after the allergic reaction, but later it might be negative. Nevertheless, the authors conclude that the skin tests with penicillin should be done in all patients in whom the history suggests the possible presence of penicillin allergy. Control tests with the vehicle should always be done to exclude possible occurrence of a false positive reaction. They stress that a negative skin test does not exclude penicillin allergy and, therefore, the possibility of a reaction to a subsequent administration.

Berger and Eisen[16] did procaine penicillin skin tests by scratch, intradermal and patch methods on 1,000 patients, some of whom were known allergic individuals, some, non-allergic individuals, and others, penicillin-sensitive individuals. There were twenty-four positive reactions which had no relationship to the group tested. In other words, they found there was no correlation between positive skin tests and clinical sensitivities and, therefore, feel that testing is not a reliable way to determine penicillin sensitivity.

Mosko et al[179] studied cross reactions between penicillin O, penicillin G, penicillium, trichophytin by means of intracutaneous skin tests on one hundred and nineteen patients. From their results they conclude that cutaneous reactivity to penicillin O and G is approximately identical for both immediate and delayed types of sensitivity and therefore one form cannot be substituted for the other in the penicillin sensitive patient. There is no correlation between cutaneous reactivity to penicillin O and G and to penicillium or to trichophytin. In the same person there is no correlation between the immediate and delayed types of cutaneous reactivity for all these four allergens and there is no correlation between the previous administration of penicillin as determined by history and cutaneous reactivity to either O or G penicillin. There was also no correlation between former penicillin reactions and cutaneous reactivity. However, from a practical point of view the presence of a positive skin test is a warning against the use of penicillin.

Mathews et al[168] question the statement in the literature that antihistamines given at the time of penicillin injections will cut down on reactions. They did a rigidly controlled experiment involving the use of antihistamine given at the time of 2,299 courses of penicillin in the same

number of patients. Follow-up was achieved in all but one hundred but the major part of the analysis is confined to the 1,922 courses of penicillin given only by injection. The antihistamine was sometimes given by injection and sometimes by mouth following the penicillin. All patients were followed closely for a total of three weeks after the last injection and they conclude that there is no evidence that oral and/or parenterally administered antihistamine produced any significant effect on the incidence of delayed or severe penicillin reactions, although there was a reduction of early reactions particularly those of the urticarial type.

Coleman and Siegel[50] studied the effect of including Chlor-Trimeton along with an injection of penicillin into a sensitive individual by making use of the contralateral passive transfer reaction to penicillin. In this they injected serum of an acutely sensitive patient into one arm of several recipients and then gave an injection of penicillin into the other arm and observed the reactions. Subsequently a similar experiment was done with Chlor-Trimeton alone with the penicillin and similar experiments were done on nine sensitized subjects who were injected with 1 ml of a solution of crystalline potassium penicillin containing 5, 50, or 500 units in order to find out the smallest dose of the antibiotic needed to elicit a contralateral passive transfer reaction. They found that the antihistamine along with the therapeutic dose of penicillin had no significant effect on decreasing the contralateral passive transfer reaction. When the antihistamine was used in smaller doses of penicillin in the sensitive subjects they found very little preventive action. They concluded, therefore, that the mixture of antihistamine drug and penicillin will not prevent severe immediate allergic shock or anaphylactic shock from developing in an extremely sensitive patient.

FitzGerald and Irvine[83] treated twenty-three patients with allergic reactions to penicillin with ACTH and/or cortisone. All patients responded to therapy. Recurrences occurred in four with allergic reactions to penicillin but most responded quickly on resumption of therapy. It is concluded that this is a safe and adequate method of treatment of this condition.

O'Driscoll[184] reviews the literature on desensitization to penicillin and reports the case of a nurse who was so sensitive that she had to give up her work. She was desensitized starting with a dose of 200 units intramuscularly and working up on the 27th injection, most of which were given at daily intervals, to one million units. Antihistamines usually intramuscularly were given to control reactions. The desensitization was so effective that she could return to her work without further trouble even though she was using penicillin a great deal.

Coleman and Siegel[49] report a patient who received penicillin by injection several times without reaction and then had a generalized reaction following the ingestion of penicillin tablets. Subsequently she had a similar episode following an injection of testosterone mixed with procaine

hydrochloride. It was subsequently found that this reaction was due to contamination of the syringe used with penicillin. Studies made on the water from the sterilizer of the physician who had injected the testosterone showed by passive transfer test that there was enough penicillin contaminant in the water to produce passive transfer reactions. Similarly, penicillin would elicit positive reactions in the passive transfer site even after it had been boiled for as long as sixteen hours, thus indicating that the penicillin in the sterilizer could still produce reactions at the passively sensitized site. Similar studies showed that once a syringe had been used for penicillin it was very difficult to remove the penicillin contamination even if the syringes were washed repeatedly, particularly if they were sterilized in the sterilizer with the plunger left in the barrel. The authors therefore have concluded that syringes are commonly contaminated with penicillin and if they are used to inject a drug into a patient who is acutely sensitive to penicillin the reaction may result from the penicillin and be attributed to the drug which is injected.

McLean[171] surveyed milk samples which contained penicillin. Two previous surveys in 1955 and 1956 of 474 samples throughout the United States showed penicillin to be present in 11.6 per cent, in concentrations varying from 0.003 to 0.08 units per millilitre. In the third survey there were 1,706 samples with penicillin in 5.9 per cent. The opinions of thirty-one allergists were that this is probably not enough penicillin to sensitize a non-sensitive patient but is enough to produce an acute reaction in an exquisitely sensitive patient, and, therefore, the food and drug law should be amended so that dairy cows producing milk are never given slow absorption penicillin and that milk should not be sold to the public from sick cows receiving penicillin or other antibiotics for at least six days from the last dose.

SALK VACCINE

Bierly[20] reviews the details of preparation of the Wyeth poliomyelitis vaccine with a complete list of the ingredients. Essential ingredients are medium 199, horse serum in a final concentration of one part in five million, phenolsulfonphthalein 0.002 per cent, soluble monkey protein derived from blood or kidney, antibiotics, which in the initial preparation consist of penicillin G, neomycin and dihydrostreptomycin, but later on when these have been practically removed they are replaced by polymixin B and dihydrostreptomycin to bring the final concentration to 50 units of polymixin B and 1/10 mgm of dihydrostreptomycin per cc. In a discussion of the possible allergenic effects the author reports that in the ten to fifteen million children who have received Salk vaccine they have not heard of any reports concerning severe anaphylactic reactions, but urticaria, angioneurotic edema, and less mild skin reactions and mild febrile reactions have been reported. While it is possible that in extremely sensitive individuals there is enough penicillin to cause reactions it is felt

that the other constituents are either in too small a concentration to cause difficulty or else are so non-allergenic that they are not apt to cause difficulty.

Siegal[228] studied the penicillin content of poliomyelitis vaccine on sixteen acutely sensitive adult allergic patients. Intracutaneous tests with undiluted vaccine on the sixteen patients were negative or plus-minus in fourteen and 1-plus in two. Eleven of the sixteen received subcutaneous injections with 1 cc of the vaccine and there were no local or constitutional reactions. Skin tests on a patient known to be sensitive to penicillin with both the vaccine and penicillin solution known to contain 10 units per cc demonstrated that the vaccine contains penicillin in a concentration of less than 10 units per cc. By passive transfer tests using the serum of a patient who had had a severe anaphylactic reaction to penicillin and with whose serum a definite positive reaction to penicillin could be obtained with penicillin in a concentration of 0.5 units per cc it was shown that the penicillin content of the vaccine was less than 0.5 units per cc. The author concludes, therefore, that the vaccine should offer no hazards either to the person allergic to penicillin or as a source of newly acquired penicillin allergy.

Lipman[147] reports a total of 490 reactions to Salk vaccine. In 304, the reactions occurred following the first injection in 1,668 cases, in 168, reactions occurred following the second injection in 1,294 cases. After eliminating the group which appeared to have respiratory infections, sore arms and miscellaneous nonallergic reactions, there were 106 patients who fitted the picture of allergic reaction, an incidence of 2.5 per cent. Children with no history of allergy had not been included in this group. In an office group of 370 patients, which included allergic children, there were only four definite allergic reactions, an incidence of 1 per cent.

Crepea[58] reports a nine-year-old boy who had asthma and had previously had allergic symptoms including asthma when visiting the zoo, particularly the monkey house. When he was given his first injection of poliomyelitis vaccine he had asthma and a month later the second dose produced the same reaction with minimal local reaction. He tolerated penicillin perfectly well and a 1:10 dilution of poliomyelitis vaccine gave an immediate skin reaction and a 1:5,000 dilution of Macaca rhesus serum gave a marked immediate reaction. A similar test with horse serum 1:100 produced only a slight reaction. It is concluded that the reaction was caused by allergy to monkey protein.

AMINOPHYLLINE TOXICITY

Considerable has been written on aminophylline poisoning and since this drug is used so widely by allergists it is very important to us. Reports on aminophylline toxicity have appeared by Rounds,[212] Love and Corrado,[152] Veum and Schwartz,[259] Jacobziner,[129] Tindall et al,[247] and by White and Daeschner.[268] The latter authors emphasize that amino-

phylline toxicity is definitely potentiated by ephedrine and that there is a doubling of the toxicity of aminophylline by the administration of a relatively small dose of ephedrine. These authors suggest a dose of aminophylline of 3.5 mgm per kilogram of body weight for intramuscular and intravenous use, 5 mgm per kilogram for oral therapy and 7 mgm per kilogram for rectal therapy. Doses should not be given more often than every six hours and preferably at seven and eight hour intervals.

Soifer[233] reviews the literature on this subject and adds cases of his own, bringing the total of reported cases to thirty-seven cases of aminophylline toxicity in the pediatric age group with eleven deaths. He emphasizes that if restlessness or vomiting appear the drug should be stopped immediately since restlessness is the constant symptom and the earliest warning of danger and vomiting is also an early symptom and can become quite serious.

Glaser and Berman[97] point out that in using this medication over a period of more than twenty years they have not had a single death or any serious toxic reactions. Since vomiting is an early sign of toxicity they never give the drug to a vomiting patient and always discontinue it if vomiting begins in a patient receiving the drug. They feel that the dosage schedule recommended by White and Daeschner is probably satisfactory but emphasize that in some suppositories the drug is not uniformly distributed and therefore one-half suppository may not contain one-half the drug.

ALLERGY AND TOXICITY TO OTHER DRUGS

Brown[33] discusses the papers which have been published on reactions to the broad spectrum antibiotics and discusses the defects in reporting of these reactions by many others. He reviews the literature on Terramycin which has been published in a five-year period in very great detail and includes in the paper some very useful tables which make reference to untoward reactions to Terramycin very easy. In a subsequent similar paper,[35] he gives the same type of information for Aureomycin and Chloromycetin.

Bernstein and Klotz[18] list the various tranquilizing drugs which are on the market and discuss the allergenicity to these drugs, particularly to reserpine, chlorpromazine and meprobamate. Reserpine has been reported to cause skin rash, urticaria, nasal stuffiness, malaise, leg ache, depression and skin sensitivity, the latter in experimental animals. Chlorpromazine has been reported to cause nasal stuffiness, dermatitis which can be of the contact type also, photosensitivity, pruritis, influenza-like syndrome, agranulocytosis, jaundice and laryngeal edema. Meprobamate has been reported to cause angioneurotic edema, urticaria, erythema, fever, arthralgia, purpura, both thrombocytopenic and non-thrombocytopenic, bronchospasm and cardiac arrhythmias.

Hollister[122] reviews the complications from tranquilizing drugs including allergic or toxic reactions which include jaundice, agranulocytosis, purpura; dermatitis, either systemic, photosensitive or contact; asthma and angioneurotic edema.

Nichols[182] reports an eleven-year-old girl who became allergic to insulin. Her symptoms consisted of edema, urticaria, and weight gain and followed the use of either beef, mixed regular or crystalline insulin, thus indicating that the allergy was to insulin itself. Local cutaneous allergy appeared within eighteen hours of the first dose she had received. The generalized symptoms appeared five days later. She responded quickly to the use of boiled regular insulin which was followed by diuresis and weight loss and disappearance of the urticaria. She was eventually desensitized to insulin enabling her to carry on with NPH insulin.

Rose and Barron[211] report an adult who had been receiving intermittent treatment with insulin for shock therapy. Following an intravenous injection of 160 units of soluble insulin after a brief rest from treatment, he went into acute anaphylactic shock which responded slowly to treatment. Skin tests with insulin from the same batch produced strongly positive reactions and similar positive skin reactions were given by all other types of insulin tested. Control tests were normal by intradermal test with pig, beef and mutton proteins. Passive transfer tests were positive using four nonallergic subjects.

Lowell[154] reviews allergic reactions to the sulfonamide and antibiotic drugs and summarizes the whole subject in table form. He also discusses skin tests, treatment and methods of prevention.

Walton[263] reports a series of eighty-three adults with aspirin allergy. These were taken from 4,761 allergic patients, giving an incidence of 1.74 per cent. Of these patients 2,580 had asthma and seventy-eight of these were aspirin sensitive. Patients with mild or relatively mild asthma sometimes had only urticaria or rhinitis from aspirin but the more severe asthmatics manifested asthma from ingestion of aspirin. However, some of the mild asthmatics developed a very severe asthma with aspirin. The overall mortality was at least four times the expected mortality in the asthmatic population, implying that when aspirin sensitivity in severe asthmatics occurs the prognosis is poor. Although the aspirin-sensitive asthmatics tend to fall into the intrinsic group, there were many in whom the asthma was definitely extrinsic in character. Although aspirin sensitivity is most frequently manifested by asthma it may also produce allergic rhinitis or urticaria.

Bridges et al[32] report an incidence of allergic reactions to novobiocin of 12.7 per cent in 308 patients. The reactions consisted of angioneurotic edema, urticaria, papular eruptions, serum sickness, fever and increased bilirubin. The authors report four cases of their own, three of whom had generalized rashes and one a fatal outcome from the use of the drug. Therefore, they warn against widespread use of this drug.

Tetreault and Beck[243] report an adult who went into acute anaphylactic shock following an intramuscular injection of thiamine chloride. The patient recovered. He had received a similar injection five years previously.

Mauer et al[169] report a mother who had received quinine twice previously and also just prior to delivery of her baby. Both the mother and newborn infant suffered thrombocytopenic purpura. This was found in both cases to be due to platelet agglutination and in vitro this was found to occur in the presence of quinine, presumably due to the presence of antibody in the plasma both of the mother and infant. Five months later the antibody was still demonstrable in the mother, although lacking in the infant, and it was believed that the purpura was the result of transplacental passage of antibodies and quinine from the mother.

Ratner and Flynn[203] studied the allergic properties of piperazine citrate (Antepar) in guinea pigs, because of reports of twenty-seven allergic dermal reactions following the use of this drug in humans. However, of the twenty-seven cases in humans eight had insufficient data reported, eleven manifested symptoms which appeared to be unrelated to the drug and eight appeared to have a serum sickness like reaction. In a relatively large number of experimental animals there were no generalized or dermal reactions noted and the authors feel, therefore, that this is a nonallergenic drug and that in the reported cases the hives must have been due to other causes.

Borrie[29] reports six cases of purpura in adults following the use of carbromal. This drug caused weakness of the capillary walls with resulting increased capillary fragility but there was no effect on the formed blood elements. Improvement occurred within a few days to a week of stopping the drug. Five of these six patients had severe itching associated with their rash.

Reichelderfer et al[205] review the literature on Benadryl poisoning and report a case of an eighteen-month-old infant who accidently ingested 350 mgm of Benadryl. The patient manifested signs and symptoms of hyperthermia, severe convulsions, cortical blindness and marked regression of the developmental pattern. She was treated with gastric lavage, reduction of hyperthemia, control of convulsions with barbiturates, control of respiration by endotracheal intubation with artificial respiration and the patient recovered completely, although it took several months to regain the loss of developmental progress.

Two general papers on drug allergy and drug toxicity have been written by Brown[34,36] and in the latter paper there are discussions on sulfonamides, penicillin, the anti-arthritic agents and chlorpromazine.

Alexander[4] has written a very systematic and complete review of the subject of drug hypersensitivity in book form. This is a book which can very readily be used for reference to look up either the reactions of any particular drug or to work in the other direction, starting with a particular lesion and determining which drugs are apt to cause it.

FOOD AND DIET MODIFICATIONS

Ratner et al,[204] from a history of soybean allergy, feel that soybean is a weak allergen and that the few cases of sensitivity to soybean which have been reported in the literature were sensitized by prolonged inhalation of the soybean dust, rather than through ingestion of the protein. By using the dual ingestion passive transfer test the authors studied several different soybean preparations on the market, some of which had been heated and some of which had not been heated, and from the results of these experiments conclude that the proper processing of soybean protein by adequate heat in the presence of moisture reduces whatever allergenic properties are present. On the other hand, inadequate heat and direct spray drying of the unheated liquid soybean mixture did not reduce the allergenicity to any noticeable degree. However, they found that soybean protein which was adequately heated in the presence of moisture and then spray-dried was hypoallergenic. They did not find soybean oil, soybean sauce, and corn soy cereal to be allergenic at all. They conclude, from the allergic standpoint, a properly modified soybean preparation is an ideal hypoallergenic substitute in the case of a person sensitive to the casein fraction of milk.

Ratner and Crawford[199] sensitized guinea pigs by intraperitoneal injections of soybean extract and later gave them shocking doses intravenously. This was done both on animals who had been fed rat rations containing soybean and also on animals who had been on soybean-free rations and whose mothers during their pregnancies had been on soybean-free diets. They also did inhalation experiments with dry defatted soybean flour on other guinea pigs and the results of all these studies showed that soybean has very low allergenicity and sensitization was not materially increased by multiple sensitizing injections.

Blue[25] reports on the use of powdered leaves of the plant Canada Fleabane incorporated into soybean formulas to prevent diarrhea. The remedy was used on twenty-five infants and young children who were on Mull-Soy and who had diarrhea from the Mull-Soy, and this preparation immediately stopped their diarrhea. After treatment for several weeks to three months, all the patients were able to tolerate the Mull-Soy in normal strength without having diarrhea, even though the herb was removed from the formula.

Howard et al[125] fed Mull-Soy to rats as a sole diet except for supplemental iron and vitamins and found that there was excellent support of growth and reproduction and lactation in the white rat for at least three generations. The same experiment was done with dried whole milk but it could not be followed through because of the high mortality in the second generation, and the copper and manganese deficiency in the milk prevented successful reproduction in the third generation.

Collins-Williams[56] fed powdered Sobee to twenty-five infants varying in age from one week to twenty-three months. The formula was well

taken by twenty-three of the twenty-five infants. One infant took it only mixed with cereal and one refused to take it at all. The infants remained on this feeding from one-quarter to five months. Weight gain was satisfactory in all cases. The stools were normal in color and soft in consistency. No untoward symptoms were observed and the product, therefore, is considered to be suitable as a milk substitute in infants.

Kane[135] fed liquid Sobee to 102 infants under nine months of age because of sensitivity to cow's milk. The milk substitute was found to be completely adequate and 90 per cent of the infants could take cow's milk at six months of age.

GASTROINTESTINAL ALLERGY

Wessel et al[267] report a study on colic or paroxysmal fussing in infants carried out in a rooming-in project. During this experiment they observed in detail ninety-eight infants, fifty of whom were classed as contented babies, forty-eight of whom were classed as fussy babies. They define a fussy baby as one who, otherwise healthy and well fed, has paroxysms of irritability, fussing or crying lasting for a total of more than three hours a day and occurring on more than three days in any one week. If an infant had no such paroxysms or the paroxysms were less than the above in total duration he was classified as contented. These babies were observed in great detail throughout the first year of life. A detailed history of allergy in the families was also taken. The fussy group was similar to the contented group with regards to details of feeding, birth weight, weight gain, sex, educational level of the mother and family history of allergy. In six of the forty-eight fussy infants fussing was remarkably reduced by the removal of a specific food, either by limiting the mother's diet in the case of breast-fed infants or by changing the protein in the artificially-fed infant. Fussiness promptly returned when the food was again ingested and this seemed to indicate an allergic etiology in the six infants. Of the forty-eight fussy infants, family tension was judged to be an important contributing cause in twenty-two, allergy in six, both allergy and family tension together in nine, and in eleven there was no apparent cause.

Martin[164] reported an incidence of 36 per cent for colic in 814 infants seen in private practice. Of the infants of allergic families, 60 per cent suffered from colic, of the infants of nonallergic families, 25 per cent, and of infants born to a mother and father both of whom suffered from major allergies, 78 per cent suffered from colic. Therefore, he feels that allergy plays a very prominent role in the causation of colic. However, he found that even some of the infants with colic from allergic families did not show relief of the colic when put on hypoallergic diets. His own treatment of colic is to put the infant on soybean formula, synthetic vitamins, sedatives, sometimes calcium and sometimes progesterone.

In this paper the author does not state how many of the colicky infants

responded to hypoallergic diets and this would be one of the best criteria for determining whether or not the colic was really due to allergy.

Glaser et al,[96] in a panel discussion by various authors including general pediatricians, pediatric psychiatrists and pediatric allergists, cover the problem of colic in all its aspects. Evidence given in favor of allergy is the family history of allergy, response to milk substitutes, experimental x-ray studies, the history of severe colic in children who later develop asthma, positive skin tests, coexistence of other allergic manifestations, stools containing mucus, eosinophiles, and sometimes blood, the higher incidence of colic in allergic than nonallergic families. On the psychosomatic side, some of the authors feel that family tension is undoubtedly a common cause, although it is difficult to evaluate whether it is the cause or the result of the colic in many cases. The dramatic response to the use of the pacifier is in favor of an emotional origin as is also the beneficial effect of increased attention by rocking, patting, and walking the infant. One of the authors found 75 to 80 per cent of colicky babies responded to the pacifier. Other causes for colic put forward are: poor feeding technique, hunger, intolerance to carbohydrates in the formula, intolerance to butter fat in the formula, organic causes and constitutional factors. The various treatments suggested include: paragoric, antihistamines, antispasmodic drugs, phenobarbitol, tranquilizing drugs, pacifiers, enemas, amphetamine, removal of allergenic foods particularly cow's milk, the use of milk substitutes, the use of denatured foods, reassurance of the patient's parents, having someone other than the mother partake in the care of the infant so that the mother can get increased rest, better feeding techniques, increased feedings, decreased feedings, removal of carbohydrates from the formula, removal of butter fat from the formula. The general conclusion of the panel is that colic has a great many causes and it is the duty of the pediatrician to attempt to find the cause and treat it as specifically as he can.

Taylor[241] reported one hundred cases of patients with infantile colic and one hundred without infantile colic, studied in detail. He concludes that it is unlikely that the sex of the infant, type of feeding, seasonal variation or allergy influenced the onset or severity of the colic but the onset or severity of the colic would appear to be related to age, birth order or time of day and the emotional state of the mother. The babies with colic gained weight more rapidly than the control babies.

Breslow[31] in a study of ninety infants seen with typical colic found that 10 per cent were due to milk allergy and the remainder to other causes.

Several papers have occurred on the question of wheat allergy and its relation to celiac disease and sprue. Roberts[207] reported two adults with nontropical sprue who gave complete remissions on wheat-free diets.

VandeKamer and Weijers[257] state that they have shown that the protein fraction of wheat, in particular gliadin, is the responsible factor for

making patients with celiac disease worse. They do not think that the harmful effect of gliadin is caused by the lack of any amino acid, since a diet rich in milk protein does not protect celiac patients from the bad influence of wheat, and, therefore, they investigated the effect of glutamine which is present in gliadin in an abnormally high proportion, namely 43 per cent. To test this, they fed glutamine by mouth for a period of six weeks to two six-year-old celiac patients who were in good condition on a wheat-free diet and no bad effects were observed, proving that glutamine in the form of a free amino acid is not a toxic substance but not proving that glutamine, as found in protein, does not exert a harmful influence. Therefore, they treated the gliadin chemically by hydrolizing it by boiling it with normal hydrochloric acid for forty-five minutes. In this way 90 per cent of the glutamine was dissociated into glutamic acid and ammonia, but, otherwise, they felt that the gliadin was unchanged except that it now contained glutamic acid instead of glutamine. After the substitution of gliadin by the equivalent amount of the deaminated gliadin a one-and-one-half-year old girl completely recovered on two occasions it was tried and the steatorrhea decreased. The second patient, a boy of eight years, was a very severe celiac showing considerable clinical improvement when the gliadin was replaced by the deaminated form, but the improvement did not persist. Therefore, they further treated gliadin by hydrolizing it with normal hydrochloric acid for two hours instead of forty-five minutes which further deaminated the gliadin to a degree that only 3 per cent of unchanged glutamine was left, and the clinical improvement was now clear and steatorrhea decreased sharply. Therefore they feel that the glutamine in the bound form is the cause of the deleterious effect of wheat and they feel that the foodstuffs, having a high ratio of amid-nitrogen to non-amid-nitrogen, are deleterious. They list the proteins according to this ratio and conclude that all the proteins that are harmless have amid-nitrogen figures of 11 or less, whereas proteins with higher values such as oats, barley, rye, gluten in wheat flour, gluten and gliadin are harmful.

One cannot help wondering whether the boiling with hydrochloric acid did not change the gliadin, as for example, we definitely see a change in proteins even by boiling in water. For example, egg white which has been heated very frequently does not cause allergic reactions, whereas the raw form causes serious allergic reactions.

Weijers and VandeKamer,[266] following their previous paper, studied the blood glutamine content after oral administration of gliadin. To do this they did a gliadin tolerance test on celiac patients, both on and off wheat diets and on controls. They found in the normal children there was little change in the blood glutamine level, whereas in the celiac patients, either on or off wheat diets there was a considerable rise with the peak at two hours. These studies were done on children who had been fasted for twelve hours and who had fasted throughout the test. They claim that

an increase of the blood glutamine content of more than 50 per cent is indicative of sensitivity to wheat. They feel that the gliadin tolerance test can be used as a means to determine wheat sensitivity.

One cannot help wondering whether these authors are using the word sensitivity in the sense that most allergists use it. It would appear that this experiment shows that the increased blood glutamine level in celiacs merely represents an increased absorption of glutamine in celiac patients as opposed to non-celiac patients.

Sheldon[225] studied eighty-six cases of celiac disease treated with a gluten-free diet. Forty-six were maintained on the gluten-free diet for a period of two years. In ten a normal diet was reintroduced after twelve months, and in thirty a gluten-free diet was maintained for more than two years. When gluten was reintroduced sixty-four cases showed normal progress. In five cases there was a return of the celiac symptoms, but in seventeen cases there was retardation of growth only which would have been missed if careful growth studies were not being done. When gluten was reintroduced, growth was not accelerated but either continued at the same speed or became retarded. The author feels, therefore, that each child has to be individually evaluated to decide whether a gluten-free diet must be continued. He cannot give an explanation as to why gluten in some children will check growth without calling forth the other symptoms of celiac disease and feels that this depends on a mechanism different from that which accounts for the other manifestations of the disease.

Finlay and Wightman[81] report twenty-seven adult patients with various specific types of malabsorption, fifteen with the primary disease and twelve with secondary disturbances. One group was treated with cortisone 125 mgm daily in divided doses by mouth with other adjunctive treatment such as a vitamin D, liver extract and folic acid, the dose reduced as they improved, and often they could be maintained on 25 mgms of cortisone daily. Another group was given a gluten-free diet. Some patients were given both treatments. With some using the gluten-free diet it was necessary to exclude all sources of gluten. Foods containing gluten are listed as meats, frankfurters, sausages, bologna, meat loaf, thickened sauces or gravy, cereals, all grains except rice and corn, bread, rolls, dumplings, pancakes, cake pastry, cookies, crackers, arrowroot, yeast cakes, dressings, spaghetti, macaroni, etc., tinned foods, cream, noodle and barley soups, commercial sauces, ketchup, mustard, salad dressings, mayonnaise, confectionery chocolate, malted milk, chewing gum and ice cream. Patients were considered to benefit from the treatment if they had relief from gastrointestinal symptoms, weight gain, reduction in fecal fat and, in many cases, relief of other defects. One case of tropical sprue made no response at all. However, of the other twenty-six patients there were fourteen of the idiopathic type and twelve of the secondary type. Of the idiopathic group seven were benefited

by cortisone alone, five by cortisone plus a gluten-free diet, one by a gluten-free diet plus cortisone and ten with the gluten-free diet alone. Of the twelve secondary types, five were benefited by cortisone alone, two by cortisone plus the gluten-free diet, one by the gluten-free diet plus cortisone and five by the gluten-free diet alone. Detailed case reports are given in many instances. Results were unsatisfactory in two patients with the secondary type of disease where the underlying disease was progressive, but satisfactory improvement was made in the remaining patients in both groups. The response to cortisone was rapid but less complete than that to the gluten-free diet and combinations of the two treatments appeared to be advantageous in severely ill patients.

Rowe et al[213] reported twenty-six adults and four children who had chronic troublesome diarrhea due to food allergy. They had had the diarrhea on an average of seven-and-a-half years. All other causes of diarrhea were eliminated. Some of the patients had other manifestations of allergy. Skin tests were not found to be helpful. Milk was the most common food involved occurring in twenty-four cases and being the sole cause in three. A great many other foods were involved in individual cases. Egg was uncommonly involved. The authors feel that when a diet, excluding the foods causing large skin reactions or foods suspected through history, fails to relieve the diarrhea the patient should be put on their standard fruit-free elimination diet or minimal fruit-free elimination diet.

Schoenkerman[219] reported eighty-eight infants investigated for regurgitation. He found that fifty-five of these stopped the regurgitation immediately by being on only soybean and water with milk and all other foods being removed from the diet. In the remaining thirty-three which continued to have difficulty he did not get enough cooperation to follow alterations in their diet. On reestablishment of the complete diet, which was done in stages, he found that forty-seven began to regurgitate with the restitution of milk, three with orange juice, three with wheat, one with egg, and one with a vitamin preparation. He feels, therefore, that milk allergy is a common cause of regurgitation in infancy and that these infants and the infants of allergic families should be breast fed if possible and other foods should be added more slowly than usual, the more nonallergenic foods first.

Bigler[21] states that allergy to cow's milk is not uncommon and must always be considered for a proper diagnosis to be made. When gastrointestinal symptoms due to milk allergy occurred in his series they were manifested by diarrhea alone in about 35 per cent of cases, with vomiting and regurgitation alone in 10 per cent, colic alone in 5. In other words, in 85 per cent there was some combination of diarrhea, vomiting and colic. Diagnosis depends essentially on the history. Eosinophiles in the stools are of considerable help. Skin tests with cow's milk, casein and whey are confirmatory evidence. Treatment consists of taking milk

from the diet and giving a milk substitute. The author does not recommend oral hyposensitization with milk.

Antia and Cooper[6] reported one adult with rectal bleeding of seven years' duration which was proved to be due to milk allergy. She became partially desensitized to milk by the drop dosage method to the extent she could take milk in small quantities in her tea.

Kiesewetter et al[138] in a detailed differential diagnosis of the cause of the rectal bleeding, in infants and children, include milk and other food allergies as one of the causes.

ALLERGY OF THE EYE

Hanser[112] discusses the various laboratory procedures which help in the diagnosis of ocular allergy, chiefly the conjunctival scrape smear, diagnostic anterior chamber puncture and also the results of treatment of the various types of ocular allergy.

Theodore[244] discusses the various types of conjunctival allergy and gives a very detailed description of chronic allergic conjunctivitis, dividing it into atopic and bacterial types. There is also a discussion of allergy of the cornea and of the sclera.

Waldbott[261] describes the various forms of allergy of the eye and gives a short discussion of the clinical picture and treatment of each. Donevan[68] presents a general discussion of the subject of ocular allergy.

INSECT ALLERGY

Bolam and Burtt[27] describe thirty children with papular urticaria, most of whom had suffered from the disease for several years. They were extensively investigated, chiefly from the point of view of examining their homes for the presence of fleas. In twenty-one cases fleas were found. In fifteen cases these were cat fleas, in three they were hen fleas, in one each, pigeon fleas, house martin fleas, human fleas and in the other nine cases fleas were not found. Clinical improvement after control of the fleas both by treatment of the home and of the infecting source was present in fourteen cases. The authors feel that all cases of papular urticaria are due to flea infestation and in those cases where they were not found they were present but missed by the investigators.

Burke and Jellinek[41] report a four-year-old girl suffering from Schoenlein-Henoch syndrome characterized by joint swelling, blood-tinged watery diarrhea, hematuria and later grossly bloody stools and profound shock. The joint swelling came on minutes after an insect bite which was believed to be caused by either a deer fly or wasp. The child was acutely ill, was treated with blood transfusions and cortisone in large doses followed by dramatic recovery. Although the authors do not believe they have proved that the insect bite was the etiological factor, it is quite probable that it was.

Pearlman[191] reviews the literature on bee and wasp stings going into

some detail on the chemistry of the bee and wasp venom, the types of reactions encountered and the allergic immunological considerations as well as desensitization. Seven cases of near fatal allergic reactions to these stings are reported.

Rytand[215] reports four cases of patients in whom the nephrotic syndrome appeared following a bee sting. He feels that these reactions are on the basis of a reaction to the bee venom.

Loveless and Fackler[153] used venom removed from the sacks of live wasps for diagnosis and immunization of wasp allergic individuals. Tests were done on normal subjects using the skin, eye tests and also the sting of the insect and comparable tests were done on wasp allergic subjects showing that there was a lower concentration of venom necessary to obtain the same response in these subjects. Following immunization with this venom the patient's intracutaneous and conjunctival reactions approached those of normal subjects and response to insect stings also resembled those of the control group. These tests showed that five species, the yellow jacket, the bald faced hornet, paper wasp, honey bee and bumble bee all possessed a common allergenic specificity and each venom also had a component peculiar to itself. They feel that wasp venom is a highly satisfactory immunizing agent against wasp sting reactions.

ALLERGY OF THE NERVOUS SYSTEM

Vahlquist[256] reports a study of migraine in children. He uses the classical criteria for a migraine attack. He found in a group of children ten to twelve years of age, 4.5 per cent suffered from migraine. In the group sixteen to nineteen years, 7.5 per cent suffered from it. In the former group, 1.9 per cent had their onset before six years of age, 2.5 per cent from seven to twelve years of age. In the latter group 1.1 per cent had their onset before six years of age, 2.4 per cent from seven to twelve years of age and the remainder after twelve years of age. There was no difference in frequency in the two sexes. The symptoms of childhood migraine are essentially the same as those in adults. However, single attacks are, on an average, of short duration, and nausea is more regular and intense; on occasion the whole picture may be interpreted as one of cyclic vomiting. The majority of the patients have a positive heredity, unilateral pain and nausea, and several have eye symptoms and other neurological dysfunction. The trigger mechanisms were mostly mental stress but also physical stress. Food allergy was a very rare cause.

Vahlquist also discusses a group of thirty-one children who had had their first manifestation of migraine before four years of age and some of these as early as one year of age. He feels there is a definite linkage between migraine and cyclic vomiting. Treatment of migraine in childhood is essentially the same as in adults.

Burke and Peters[42] report ninety-two cases of migraine in children. Only the allergic aspects will be considered here. They found a history

of allergy in eleven. Seven of these had allergic rhinitis and one of this group also had bronchial asthma. Food allergy was noted in two instances and two children had experienced attacks of angioneurotic edema. No significant correlation was present between the allergic symptoms and attacks of migraine, and they do not feel that allergy is a precipitating factor of migraine but rather feel that emotional stress is probably more important. They do not feel that antihistamines or the elimination of food offenders can be effective in treatment.

Thomas et al[245] review the literature on neurological complications of the administration of foreign sera and report a case of an adult who developed bilateral allergic neuronitis of the acoustic nerve after the administration of tetanus antitoxin during a bout of accelerated serum sickness. There was complete deafness, tinnitus and disturbance of equilibrium. Five months later only partial improvement had taken place.

PSYCHIATRIC CONSIDERATIONS

Marmor et al[162] studied twenty-two children with neurodermatitis, ranging in age from six months to eleven years, mostly under five years of age. In most of them the rash began during the first year of life. The study is from the psychological point of view and the results show that in most instances the child was either rejected or unavoidably separated from the mother just prior to the onset of the rash and in about one-half of the cases there was obvious or suggested rejection of the child. Neurodermatitis is felt by the authors to be a disease of adaptation and the allergic reaction can be triggered by emotional stress, physiological stress or the presence of certain allergens.

Abramson[2] describes a four-year-old child who had had eczema since three years of age. This was attributed to psychogenic factors dating from seventeen months of age when she refused to have bowel movements and had subsequently been investigated with barium enemas, etc. These events were acted out during therapy and the eczema cleared completely six weeks later. At the age of five years following another psychologically dramatic episode she developed rash again. The author feels that in this case the allergic components were negligible compared with the psychogenic components and that this is a case of essentially psychogenic eczema.

Tec[242] reports a six-year-old boy with both very severe atopic dermatitis and schizophrenia. There were many very severe psychiatric elements present and he was definitely worse at times of emotional stress. The author feels this eczema had a very definitely psychogenic etiology.

Woodhead[273] also advances the theory that eczema is caused by a disturbed mother-child relationship and is a direct cause of suppressed hostility of the mother toward the child.

Miller and Baruch[174] discuss a group of 201 clinically allergic children, practically all of whom had or had had asthma. Skin tests showed

that a great majority were immunologically allergic or else clinically allergic. In every instance the parents were interviewed. The authors feel that in a great many cases the asthma was either caused or aggravated by rejection of the children by the parents, and they feel this rejection usually antedated the onset of the asthma, rather than being the result of it. They feel these factors should be kept in mind for the proper handling of allergic children. These same authors[173] report a three-year-old boy suffering from asthma who had positive skin tests to practically all the pollens and many positive reactions to other inhalant substances and numerous foods. He was treated from a psychosomatic point of view and at no time were restrictions placed on his diet or physical environment, and no specific allergy treatment was given. He was observed for a year, during which time he had twelve episodes of wheezing, each one related to his being angry, mostly because of lack of affection from his parents and his suppression of this anger. At times when he became angry and gave vent to his anger no asthma resulted. By intensive psychotherapeutic play sessions with the child and psychotherapy with the parents considerable improvement was brought about. The authors feel the positive skin tests were an immunological response to previous exposure to allergens but feel that the emotional problems were expressed as asthma not due to the allergens which gave positive skin tests.

Harris and Shure[114] review the literature on the emotional factors in asthma and report a study carried out on school children between the ages of six to twelve years. These children were studied intensively and their emotional make-up evaluated in each case by their teachers who made the observations independently of the study without knowing whether the children had asthma or not. There were twenty-five children in each group and they were found to have essentially the same emotional make-up, although of course there was a wide variation throughout each group. The authors conclude that there is not a specific behaviour pattern such as paternal rejection, etc., peculiar to the asthmatic child.

Shivers[226] also feels that emotional aspects must always be considered if one is to treat the allergic child completely. He feels that mothers of these children are usually very serious people who find child up-bringing a very difficult matter. They overprotect them and show considerable concern. The allergic children themselves, on the other hand, tend to be shy and lack self-confidence. The fathers are very often quiet people, not actively interested in the child's activity. He feels that in many cases these emotional factors play a considerable role.

MISCELLANEOUS

Dent[63] discusses the causes of eosinophilia in children and lists them in table form. He points out that the syndrome of visceral larval migrans is probably the most important single cause of a sustained high eosino-

philia in children with or without accompanying constitutional symptoms. The clinical picture of this syndrome is described in detail.

Stafford[234] reviewed 1,107 differential blood counts done on 861 patients, all children. In the nonallergic group, consisting of 674 patients, on whom 841 differential counts were done, the counts were normal in all but 17 per cent, which showed an eosinophilia of 6 per cent or more. Of the 187 patients in the allergic group eosinophilia was a great deal more common. The author points out the presence of otherwise unexplained eosinophilia should arouse suspicion that the child is suffering from some form of allergy but allergy cannot be diagnosed on this alone.

Collins-Williams[54] reviews the symptoms which have been ascribed to milk allergy in the literature and reports a case of an infant who showed an acute allergic or anaphylactic reaction to evaporated cow's milk. He reviews the literature on the subject, listing the thirty cases, including his own, which have been reported to have shown these acute reactions to cow's milk. These are analysed in detail according to age at the time of shock, type of cow's milk producing the shock, skin tests with goat's milk and cow's milk, whether other allergies were present at the time, etc. He finally discusses the methods of preventing this syndrome in infants.

Collins-Williams[55] reviews a consecutive series of 3,000 private pediatric patients in order to assess the incidence of milk allergy. If one excluded the patients who were seen at anytime for major allergy or those who were referred as allergic patients, the latter being omitted since this would give an undue weighting to the series, there was an incidence of 0.3 per cent. The diagnosis of milk allergy was made on the basis of clinical symptoms, and proven by the removal of milk from the diet producing a remission of the symptoms, addition of milk to the diet bringing the symptoms back and the symptoms disappearing when milk was withdrawn again. The cases reported presented syndromes such as vomiting, diarrhea, severe buttock rash, colic, melena, celiac syndrome, severe behaviour disorder and acute anaphylactic shock. The author stresses that although this incidence is relatively low, it is great enough that the practicing physician should consider milk allergy in the differential diagnosis, particularly in infants suffering from a wide variety of symptom complexes, both gastrointestinal and otherwise. Otherwise the diagnosis will be missed in most cases.

Gruskay and Cooke[105] administered purified egg albumin to twenty-one infants recovering from diarrhea and to nineteen control subjects of the same age group suffering from diseases other than gastrointestinal disease and measured the concentration of egg albumin in their sera by the precipitin method. They found that in the controls there were evidences of slight permeability of the gastrointestinal tract to this whole protein and in the study this was 0.02 per cent of the ingested dose, but this was markedly increased during diarrhea, being approximately 0.1 per cent of

the ingested dose. After recovering from the diarrhea there was a significant reduction. The authors conclude from this that in diarrhea there is an increased absorption of unaltered proteins through the gastrointestinal tract, and it is recommended that these infants, during the treatment of their diarrhea, should be fed on a hypoallergenic food to try and prevent them from developing other symptoms.

This is an excellent study since it is quantitative and most such studies which have been done have been chiefly qualitative by means of the Prauznitz Kustner reaction. This experiment thus demonstrates one method in which food allergy may be developed.

Johnstone[132] studies the effect of different doses of ragweed pollen for the treatment of ragweed hay fever in childhood. There were 112 children altogether and they were selected at random for the dosage schedule with which they were to be treated. One group received the highest tolerated dose of 1 :200 to 1 :500 dilution. One group received up to ½ cc of 1 :5,000 dilution and one group up to ½ cc of 1 :10,000,000 dilution and the fourth group served as controls and received only normal saline. All children were studied for at least two separate ragweed seasons. Most were seen during three seasons. In the highest tolerated dose group, 68 per cent who had pollen asthma before starting treatment lost their asthma and none of them who had previously had hay fever without asthma developed pollen asthma after treatment was begun. Results in the 1 :5,000 group were nearly as good, but in the 1 :10,000,000 group only 19 per cent of the children who had had pollen asthma before treatment lost their asthma and 60 per cent of this group developed pollen asthma for the first time on treatment. Among the control group only 7 per cent who had previous pollen asthma lost their asthma and 42 per cent developed asthma for the first time in spite of treatment. Therefore, it appears that the high dosage method of treatment or the moderate dosage method of treatment are both fairly effective, whereas the so-called very low dosage method of treatment is quite ineffective as far as treatment of ragweed pollenosis goes.

Boyden and Glaser[30] studied 560 children twelve years of age or younger, of whom 200 were under four years of age, with regards to food dislike and allergy to food as diagnosed by history and skin tests. They conclude from their studies that correlation between food dislike and allergic reactions to the disliked foods is extremely low and therefore that food dislikes are not helpful as an index of allergy.

Eisenberg[73] investigated the effect of certain tranquilizing drugs on allergic patients to minimize the psychological factors which contributed to them doing so poorly. Studies were done with chlorpromazine, reserpine, miltown, mephenesin and equanil. These drugs were found to help many patients but they also had side effects in many patients. The author concludes they are useful in treating these patients but are only

adjuncts and may not be used as replacement for the accepted modes of therapy.

Morrison[178] reports on a thirteen-week-old infant who suffered from continual crying and spitting-up of formula and was changed from a milk feeding to Nutramigen with cessation of symptoms. Because of the swelling of two ribs the infant was investigated and found to have infantile cortical hyperostosis and was found to tolerate cow's milk perfectly well. The diagnosis of milk allergy had been made on the basis of improvement following the removal of milk, and the author points out that the infant giving these symptoms may on occasion have infantile cortical hyperostosis.

This infant, however, should never have been diagnosed as milk allergy since the diagnosis cannot be made simply because symptoms disappear when milk is removed from the diet. The minimum requirement for diagnosis is that the symptoms return again when milk is added to the diet and again disappear when milk is withdrawn.

Heiner and Sherwin[115] report on three patients with visceral larva migrans, one of whom had very severe wheezy breathing which almost caused death and in another of whom there was mild wheezy breathing. This paper is of importance to allergists since it reminds us that visceral larva migrans must be included in the differential diagnosis of wheezy breathing. In the two cases reported the wheezy breathing was identical to allergic asthma.

Abram and Frankel[1] describe patients with extrinsic bronchial asthma who have a sudden onset of pyrexia, cough, wheezing and dyspnea who are found on investigation to have the middle lobe syndrome characterized by pneumonitis with atelectasis of the middle lobe. In the past many of these have gone on to develop bronchiectasis and required surgical removal. Four cases are described, one of which was in a child. The authors stress that if these are to be treated early medically with bronchodilator drugs, antibiotics and expectorants, complete recovery can be expected and it is not necessary for surgical treatment later.

Tuft et al[254] report on an adult who suffered from difficulty in breathing through the nose and an unproductive cough and headache as well as urticaria. He was considered to be allergic but complete intracutaneous skin tests did not give any positive reactions which appeared significant according to the history. Antihistamines gave temporary relief. It was noted that the inhalation of hydrogen sulphide fumes or the smell of cooking eggs produced symptoms. Dietary manipulation revealed that the nasal and cerebral symptoms followed the ingestion of egg, corn, garlic or certain mold cheeses, while the eating of the members of the mustard and cabbage families produced the urticaria. Studies of these foods revealed that it was those which contained large amounts of sulphur which produced the reactions. The nasal and cerebral symptoms were also brought on by the ingestion of methionine. The patient was

given three types of capsules, one containing methionine, another, cystine and the third, talc. The methionine capsules produced symptoms similar to those from eating egg. The talc capsules produced no symptoms at all and the cystine capsules produced a slight nasal stuffiness. The patient was then put on a prolonged course of aureomycin to test whether or not disturbance of the bacterial flora of the intestine would alter the reactions, and it was found that during this period egg produced no symptoms, whereas, subsequent ingestion after the antibiotics were discontinued again caused symptoms. The authors feel, therefore, that the reaction might be biochemical rather than immunological or allergic because the disturbance to the bacterial flora in the intestine would alter the method of metabolism of the methionine. However, they feel that the experiment demonstrates one explanation for instances of food allergy with positive clinical histories and negative skin tests.

Peshkin[192] presents a general discussion of skin testing in both children and adults with emphasis on the errors that can be made in doing the tests and in interpreting them.

McKay and Wahle[170] report several fatal cases in the neonatal period from an epidemic of severe gastroenteritis. The outstanding features at autopsy were distention and dilatation of the small bowel, diffuse congestion and edema of the gastrointestinal mucosa and small areas of hemorrhage and ulceration in the small and large intestines. Microscopically there was diffuse inflammation, and the outstanding pathological change was intravascular fibrin thrombosis of capillaries and precapillary arterioles in the lungs, liver, brain, spleen, adrenals and kidneys, and the more severely affected kidneys had every glomerular tuft completely occluded by a fibrin thrombus. The renal lesion was identical with that in the kidneys of rabbits with a generalized Shwartzman reaction. The authors briefly review the literature on previous reports of this reaction and conclude that what they found pathologically here is the presence of Shwartzman reaction, both local and generalized.

Malloy[161] studied twenty-four cases in which he injected antihistamine with pollen so that he could go up to a very high dose of pollen. In ten cases the antihistamine was injected one to two mms from the injection site of the hyposensitizing solution and in fourteen others it was included in the same syringe as the hyposensitizing solution. A few of these cases were dust-sensitive rather than pollen-sensitive. In twenty-one of the twenty-four cases excellent results were obtained, and it was possible to increase the dosage of the hyposensitizing material up to such a level that the patient could get good improvement.

Morrison et al[177] describe a microscratcher for making abrasions on the skin prior to the performance of skin tests. The authors believe this is a technique which combines the accuracy of the intradermal tests with the safety of the scratch tests and do not feel that after five years of use

they have obtained any additional information by giving intradermal tests subsequent to the use of the microscratcher.

Adriani[8] summarizes the effects of anesthetics on allergic patients, pointing out that in the allergic patient whose symptoms are difficult to control adequate ventilation may be difficult to maintain, especially in asthmatics and patients with hay fever, because of the secretions and spasm causing obstruction. Patients whose allergic symptoms are easily controlled and who are symptom-free are very easy to anesthetize and it is seldom necessary to alter techniques or selection of drugs. It is only when the history of untoward response to drugs exists that the possibility of allergy to anesthetic drugs must be considered. Allergy to inhalation anesthetics is uncommon. Allergy to nonvolatile drugs used for general anesthesia or drugs used as adjuncts to anesthesia is rare but has been reported. Most drug reactions are encountered with local anesthetics. Cyclopropane has a laryngospasmogenic effect and may occasionally cause bronchospasm; therefore, it should be avoided in asthmatics, but in most instances the patients tolerate the drug without difficulty. If a narcotic is necessary for an asthmatic patient, demerol is preferred. There are no objections to spinal anesthesia in an allergic patient.

Black[22] describes a test in which dried protein allergen (food, inhalant or pollen) and plasma from a sensitized or allergic patient are mixed with living leukocytes and platelets either from the patient or from a nonallergic donor and examined under a microscope while kept at 37° centigrade. If the plasma from the allergic patient contains antibody to the protein allergen which is present there are progressive cytotoxic changes in the leukocytes, loss of ameboid activity, rounding of cell contour, decrease or cessation of cytoplasmic movement and of Brownian movements of intracellular granules, increased staining and diffusion of stain from granules and vacuoles into the cytoplasm. The tests are claimed to be specific. False negative reactions are not obtained. A positive reaction does not necessarily mean clinical sensitivity, but if the reaction is prompt and strong such a sensitivity is likely. Changes are also seen in the platelets. Changes are usually seen within 15 minutes to several hours. The conclusion is that this is a very useful test for determining clinical sensitivity in a patient.

Matheson,[166] in a general discussion of allergic conditions in children, emphasized the importance of history, physical examinaiton, skin tests and specific diagnostic methods.

Halpern and Halpern,[107] by means of a questionnaire answered by fifty-six physicians, made a study of the incidence of convulsions following the administration of diphtheria pertussis and tetanus toxoid and vaccine in a five-year period. In this group of children there were fifteen convulsions, six with the first dose, seven with the second dose and two with the third dose. No child who had a convulsion had a history of

allergy. Eleven recovered completely, three had irreversible brain damage, and one died. They feel the incidence of convulsions following the DPT has appreciably decreased in the last few years. Allergy is not a contraindication to immunization. The standard methods of immunization may be applied to allergic children in the first few years of life. However, it may be advisable in older highly allergic children, who require either their primary immunization or booster doses, to administer smaller doses more frequently.

Ratner and Crawford[200,201] showed experimentally that gelatin is nonanaphylactogenic. They used different grades of gelatin, namely, crude gelatin, food grade gelatin and intravenous grade gelatin and its precursors—comminuted ossein and also bovine plasma. The studies were done using anaphylactic tests on the guinea pig and also Schultz-Dale experiments. They feel that any antigenicity attributed to gelatin is due to contamination by some blood element of the species from which the gelatin is derived. Blood contaminant in both comminuted ossein and food grade gelatin was present in such small amounts that it did not induce any anaphylactic reactions in animals sensitized to the whole plasma of the animal from which the gelatin was derived. The authors feel that any allergenicity in man which might be attributed to gelatin is due, therefore, only to contamination with these blood elements.

Christensen,[46] in a very comprehensive symposium on tetanus, sets out in some detail the methods of prophylaxis of tetanus in the absence of wounds or injuries and in the presence of wounds or injuries either in patients who have previously been actively immunized or in patients more sensitive to antitoxin. He lists in detail the method for treating such a patient who is sensitive to antitoxin by desensitizing him with antitoxin after treatment with benadryl, ACTH and epinephrin solution, as well as other medications which can be used to prevent allergic or serum sickness reactions.

Prickman and Lofgren[195] describe an emergency set for combating anaphylactic reactions which should be available at strategic points throughout hospitals and stress the need for having such a set made up ahead of time. The composition of the kit is described in detail.

Williams[269] reviews sensitivity reactions which are seen in general practice under the headings of local reactions, anaphylactic reactions and serum reactions and describes the clinical picture and treatment of each of these. He has special notes on the administration of horse serum, skin testing and hyposensitization in allergic patients and reactions to penicillin, insulin and bee and wasp stings.

Moynihan[180,181] discusses tetanus prophylaxis in a series of 7,580 patients given tetanus antitoxin as prophylaxis. There were 401 (5.3 per cent) reactions. These consisted of anaphylactic shock in two, local reaction at the site of the test or injection or both in 205, serum sickness in 192, a questionable thermal reaction in one and a questionable neuro-

logical complication in one. Reactions were more common in children but most of the series was composed of adults. Each type of reaction is discussed.

Lubens[155] studied 205 patients with poliomyelitis seen during the 1949 epidemic in New York City and ninety-five cases seen the next year. These patients were divided into allergic and nonallergic groups and in the 300 patients there were 152 in the allergic group and 148 in the nonallergic group. The incidence of bulbar involvement and of death was considerably greater in the allergic group than in the nonallergic group, both in the total series and in each individual epidemic. Therefore, the author concludes that allergic individuals are more prone to develop the bulbar form of poliomyelitis and to have a fatal termination than are nonallergic individuals who develop poliomyelitis.

Leary et al[142] point out that throughout the United States the peak incidence of poliomyelitis follows shortly after the peak incidence of pollen counts of grasses and weeds. They also found in a series of fifteen unselected successive patients treated for poliomyelitis that there was twice the incidence of positive skin tests with pollens than might be expected on random sampling of the general population. They suggest, therefore, that there is a possible relationship between poliomyelitis and pollinosis, and this must be considered as one of the factors favoring susceptibility to poliomyelitis infections along with other conditions like pregnancy, tonsillectomy, fatigue, etc.

Szanton et al[239] report thirty patients, seventeen treated and thirteen as controls, all of whom suffered from asthma precipitated by bacterial allergy, that is following respiratory infections. The asthma was also caused by inhalant substances. They were followed for two winter seasons. During the first season their upper respiratory infections and attacks of asthma were recorded and during the next season twenty treated cases were given suppository penicillin once monthly for five months during the winter season. In the treated group the attacks of asthma and upper respiratory infections were substantially decreased from that found in the controls. The authors do not feel the results are conclusive because of the small number of cases. They feel that a further trial of this type of prophylaxis is indicated. There were no allergic reactions to penicillin.

Blatt[23] presents a very complete review of bacterial allergy.

Dickson et al[67] report a study of the use of cold vaccine in 246 patients, all adults. The vaccine used was a pooled vaccine composed of a great number of organisms isolated from patients with various forms of upper respiratory infection. The survey was started on 425 patients who were selected in the sense that they were members of the staff of four hospitals and also employes and students of the same four institutions, but they were selected completely at random as to whether they got a strong vaccine, a weak vaccine or a control saline injection, and all patients were dropped from the series who did not have more than five injections, so

that only 246 patients were reported. The average number of injections given at five to seven day intervals was approximately thirteen in all groups and approximately the same proportion of good results were obtained in all groups. Approximately 45 per cent were better, 12 per cent, worse, 25 per cent, the same and in the remainder there was no information. This portion of the study, therefore, suggests that the vaccine is of no value. However, in another series of sixty-nine selected patients who were given a stock autogenous vaccine prepared similarly the results were much better, there being slight improvement in 25 per cent, moderate improvement in 36 per cent and marked improvement in 26 per cent, with no improvement in only 13 per cent. The authors feel, therefore, that in the selected cases where more careful supervision is possible than with the mass use of cold vaccine better results are obtained.

Ratner et al[202] present a very detailed study of sixty-four infants and preschool children who were thoroughly studied from the point of view of allergy. From the analysis of their data they draw many conclusions. They do not feel that allergy appears to be controlled by hereditary factors. Evidence of congenital allergy, that is, sensitization *in utero,* was found in 27 per cent of cases. In the first year there was a preponderance of eczema followed by a fall in eczema and a rising incidence of asthma and later hay fever. In the first year 100 per cent of the patients reacted to foods alone or in combination with other allergens but by the fifth year this had been reduced to 60 per cent and the inhalants and pollens were becoming more prominent. Milk sensitivity occurred in only 28 per cent and none of these patients reacted to milk alone. There were a great many reactions to egg, cereal grains with the exclusion of rice, sea foods, and citrus fruits. No patient reacted to ragweed alone and no patient reacted to grass pollen alone. Occasionally inhalants were the sole offenders. Molds always occurred in conjunction with other sensitivities. Nasal eosinophilia was found to be important and occurred in 89 per cent of patients. Thirty-one per cent of patients showed retardation of bone maturation for which they recommend thyroid. They feel that complete investigation of allergic infants is indicated and skin testing should be carried out thoroughly so that the allergy can be treated while in its early stages.

Lipman[145] reports two infants who did not have major allergies, such as, asthma or eczema, but who suffered from allergic toxemia characterized by fever, apathy, lethargy and vomiting due to food allergy. In both cases the temperature rose abruptly to 103° or 104° after ingestion of the offending food and in both cases one of the principal offending foods was milk. Diagnosis was proven in each case by trial diets and skin testing.

Glaser[92] stresses the importance of trying to prevent allergy in potentially allergic children. Eggs, foods containing large amounts of egg and cheese are eliminated from the diets of pregnant women. Not more than one pint of ten minute boiled milk is permitted per day. Breast feeding

is urged. Egg is not introduced until after the third to sixth month. A preparation other than cow's milk is used and a soybean preparation is recommended. With such procedures there is only about one-quarter the incidence of allergic symptoms as compared with the control group in later years.

Clein[48] stresses the need for early recognition of allergic symptoms and early management of these symptoms so that these infants do not grow up to be allergic cripples.

Dees[60] discusses the methods of diagnosis and treatment of allergic rhinitis and asthma in children and also the use of steroids and antibiotics in allergy. This is a very practical discussion of value to a practicing physician.

Feinberg and Feinberg[79] stress the advances that have been made in allergy during the past fifty years, pointing out that most allergic people can be helped, but there is a much greater need for complete investigation in order to accomplish this.

Glaser[91] edits a symposium which contains articles by thirteen other authors, each covering an important subject of allergy in infants and children.

Burrage et al[43] present a general article on allergy with emphasis on the diagnosis and treatment of eczema, asthma, nasal allergy, hay fever, urticaria, angioneurotic edema, serum sickness, drug allergy, contact dermatitis and some of the unusual forms of allergy.

Cohn[139] reviews the literature on physical allergy over a five-year period.

Halpin,[108,109,110] in a series of three articles, presents a miscellaneous review of allergy for 1954, 1955 and 1956 respectively.

Withers and Hale[272] review the subject of food allergy, covering most of the material published during the past ten years as well as historical articles previous to that.

Glaser[94] has published a book, *Allergy in Childhood*, which is a very comprehensive, excellent and practical book on this subject. It can certainly be highly recommended for any physician who is practicing on children.

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LOS ANGELES SOCIETY OF ALLERGY

At a recent meeting of the Los Angeles Society of Allergy, the following officers were elected to serve in 1958:

Jerome J. Sievers, M.D.....President
Ralph Bookman, M.D.....Vice President
Isadore Pitesky, M.D.....Secretary-Treasurer

RESIDENCY IN PEDIATRIC ALLERGY

Childrens Hospital, Columbus, Ohio, affiliated with the Ohio State University College of Medicine, offers a one-year residency in pediatric allergy to candidates with two years accredited residency in pediatrics. Address correspondence to John H. Mitchell, M.D., Division of Allergy, Ohio State University, Columbus, Ohio.

CUMULATIVE INDEX?

Numerous requests for a separate Cumulative Index, covering the first fifteen volumes of the ANNALS OF ALLERGY, have reached the Editorial Office. Should an index of this type be published, it would comprise a minimum of 216 pages. Before initiating this venture, the publisher would like to have some idea of what demand there might be for a volume of this type. Those readers who are interested in acquiring a Cumulative Index should write W. T. Coulter, President, Bruce Publishing Company, Saint Paul 14, Minnesota.

In Memoriam

SANFORD WILLIAMS FRENCH

Colonel Sanford Williams French was one of the early Honorary Fellows of The American College of Allergists. His devotion to his military duties was his primary commitment. The advancement of allergy in military hospitals was an all-important project of his command. Colonel French became interested in allergic diseases in 1924. When his request for training in this specialty was refused by his military superiors, the Colonel obtained a leave of absence—spending his time and own finances to obtain his initial training with Drs. Albert Vanderveer and Robert Cooke in New York City. Subsequently, Colonel French was the first and only army allergist, establishing the original army allergy clinic at the Station Hospital of Fort Sam Houston in 1927. His clinical work was productive of several original publications. Justified advancement in army rank drew Colonel French further into administrative duties and away from his clinical endeavors. His interest, however, never lagged; and in each hospital of his command the allergic patient received personal attention from the commanding officer.

Colonel French entered the U. S. Navy in 1898, serving as Chief Petty Officer until 1908. Continuous service in the U. S. Army followed his graduation from George Washington University Medical School in 1909. His military assignments included command posts in various parts of the United States, Hawaii and Panama. His retirement began on December 31, 1944 when he resumed residence in San Antonio, Texas—close by his beloved Fort Sam Houston.

In 1942, he was assigned as Surgeon of the Fourth Service Command, a position in which he served in his customary devoted fashion. The allergists in World War II will always remember the enthusiasm with which allergy services were established in the hospitals in this area. Extracts for testing and treatment were willingly supplied upon request to military installations throughout the world. This contribution of time, energy and knowledge provided relief to many allergic patients and furthered the prestige of allergy and allergists in military annals. These achievements will never be forgotten by those who were the recipients of this devotion to his duty and to his specialty. Colonel French died in Brooke General Hospital, Fort Sam Houston, August 21, 1957 at the age of seventy-five years.

L.J.H.

A. WILLIAM BANGHART

Dr. A. William Banghart, London, Ontario, with a fellow fishing companion, was drowned in Lake Erie, Sunday, August 4, 1957.

Dr. Banghart, born forty-two years ago at Dorchester, Ontario, son of the late Dr. Percy Banghart, was educated at Central Collegiate. In 1944, he was graduated from the University of Western Ontario School of Medicine. He served as an army medical officer in London and at Camp Borden from 1944 to 1947. He later became Consultant on Allergy at Westminster Hospital, an interest in which he devoted much time.

He was also on the attending staffs of Victoria and St. Joseph's Hospitals, and was treasurer and recently vice president of the London Academy of Medicine, where he was greatly interested in general practitioner instructional courses. Dr. Banghart was also a member of First St. Andrew's United Church, the London Hunt Club and Alpha Kappa Kappa medical fraternity.

He had been a member of The American College of Allergists since June 17, 1957.